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Meat... Its Place in the Dietary Management of Nephritis

The formerly held tenet that protein intake should be restricted for all patients with impaired renal function, in order to afford the kidney physiologic "rest," is no longer valid.[1] Except for infection and some neoplastic and traumatic disorders, the treatment of renal disease is nonspecific and essentially symptomatic. The clinical problem centers largely on diet regulation, in the hope of stimulating the kidneys to improve impaired function, without unduly risking harm.

Even in the presence of azotemia, a protein intake of 60 to 80 Gm. per day has not been found harmful to the renal patient. Low protein intake, on the other hand, together with urinary loss of protein may encourage the development of asthenia, anemia, hypoproteinemia, and edema.[2] Also pertinent to the dietary management in renal disease is the experimental finding that high protein diets in normal dogs promote higher urea clearance and greater renal blood flow than do low protein diets.[3,4]

Except in anuria, a protein intake adequate to maintain nitrogen balance has been suggested.[1] Although as little as 30 to 40 Gm. of protein per day may suffice for this purpose in the fever-free patient at bed rest, few occasions arise when 1 Gm. of protein per day per kilogram of body weight may not be given safely. In the presence of significant proteinuria, unless specifically contraindicated, the dietary protein may be increased beyond that amount in order to counterbalance the urinary protein loss.

Contrary to the still prevalent ancient belief among the laity, red meats are just as harmless to the renal patient as white meats; nor is there evidence that plant proteins are more beneficial in nephritis than animal proteins. As with the normal person, the dietary protein of the patient should be of high biologic value.

Meat, because of its high content of biologically complete protein, may contribute valuably to the protein needs of the nephritic patient. The nutritional importance of meat, however, is not limited to its contained protein. Meat also contributes highly significant amounts of iron and of the vitamin B complex, including niacin, pantothenic acid, pyridoxine, riboflavin, thiamine, and the newly discovered vitamin B_{12}. Other salient features of meat in the dietary of the patient are its high palatability, its stimulation of the digestive processes, its satiety value, and its easy and practically complete digestibility.

1. Mann, G. V., and Stare, F. J.: Nutritional Needs in Illness and Disease, Handbook of Nutrition, American Medical Association, ed. 2, Philadelphia, The Blakiston Company, 1951, chap. 17, p. 351.
2. Weiss, S.: Diet and Bright's Disease, Connecticut M. J. 5:496, 1941.
3. Jolliffe, N., and Smith, H. W.: The Excretion of Urine in the Dog: II. The Urea and Creatinine Clearance on Cracker Meal Diet, Am. J. Physiol. 99:101, 1931.
4. Van Slyke, D. D.; Rhoads, C. P.; Hiller A., and Alving, A.: The Relationship of the Urea Clearance to the Renal Blood Flow, Am. J. Physiol. 110:387, 1934.

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Volume 246 JANUARY 24, 1952 Number 4

THE SURGICAL TREATMENT OF PEPTIC ULCER*

FRANK H. LAHEY, M.D.,† AND SAMUEL F. MARSHALL, M.D.‡

BOSTON

SO MUCH has been said and written on the subject of peptic ulcer that one could not unreasonably ask why we are presenting a discussion of the subject to this audience. Our reasons for doing so are based on the fact that the clinic, because of its interest in this subject, has had to deal with such a large number (16,000) of cases of peptic ulcer, in which some 1600 partial gastrectomies have been performed (Table 1). In discussing numbers we are aware that the mention of numbers of cases may be construed as vanity. Such is not the case in this instance. Large numbers of cases provide something for which there is no substitute in medicine and surgery — that is, experience. From such a large experience one can reach conclusions, based at least on adequate data, on such aspects of this problem as the effects of delay on the mortality in partial gastrectomy for duodenal ulcer. It is on this experience that we wish to report.

When should surgery be resorted to for bleeding ulcer? Is the complication of the dumping syndrome a troublesome one? Has the type of operation employed (Hofmeister) with anastomosis of the proximal loop to the greater curvature proved satisfactory? What has been the effect of Banthine on ulcer patients? What place does vagotomy occupy in the surgical treatment of peptic ulcer? How common is pancreatitis in partial gastrectomy for duodenal ulcer, and how can it be avoided? What is the relation of cancer to gastric ulcer, and what are the indications for operation in recurring pyloric obstruction? We have literally lived with these problems from the very early days of peptic-ulcer surgery, and we have seen striking changes in the management of the lesions, many of fairly recent origin. These changes, operative and nonoperative, have now been in existence long enough to permit some conclusions concerning their value and place.

In order to approach this subject logically it would perhaps be best first to discuss the nonoperative management of patients with peptic ulcers, some of the changes that have taken place and some of the changes that should take place but as yet have not developed.

Co-operation between gastroenterologist and surgeon in regard to nonoperative and operative management of peptic ulcer is now well and quite satisfactorily established. However, one opportunity remains for further improvement in the medical and surgical co-operative management of patients with duodenal ulcer.

Over the years, those of us who have had to deal with surgical problems that are not primarily surgical but are referred to us by physicians after medical management has failed have often been impressed by the fact that at least some of the mortality is related to delay in the treatment of many of these diseases, such as longstanding gall-bladder disease, advanced cancers of the colon and rectum, regional enteritis after multiple skip areas have been involved, advanced stages of hyperthyroidism and many other such conditions.

TABLE 1. *Operations for Peptic Ulcer, 1931–1950.*

	TOTAL NO. OF OPERATIONS	RESECTIONS
Duodenal ulcer	1257	1067
Gastric ulcer	361	356
Jejunal ulcer	193	180
Totals	1811	1603

This is strikingly true in many of the patients with duodenal ulcer who come late to surgery. The mortality in cases of duodenal ulcer treated by partial gastrectomy is largely related to the degree of ulceration of the head of the pancreas and to the degree of involvement of the common duct as it passes through the head of the pancreas. This involvement, which indurates these structures, makes their anatomic visualization and demonstration difficult and increases the hazard of the removal of such ulcers, either by increasing injuries to the common duct in the process of removing them from the head of the pancreas or through the

*Presented at the annual meeting of the New England Surgical Society, York Harbor, Maine, September 22, 1951.
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‡Surgeon, New England Baptist Hospital and New England Deaconess Hospital.

occasional occurrence of pancreatitis following their difficult removal from the head of the pancreas. These complications could in some measure be avoided if physicians would place a more reasonable limit on the number of acute ulcer episodes or hemorrhages from the ulcer that their patients may undergo before finally urging them to submit to partial gastrectomy.

There is probably no lesion other than duodenal ulcer, with its well known history of periodicity, in which it is easier to delay operation and to permit the patient to go through repeated attacks of ulcer activity until such a chronically indurated ulcer, involving the common duct or deeply eroding the head of the pancreas, has occurred that it results in the inevitable increased hazard of the removal of such an ulcer. This is one of the psychologic situations in which it is difficult to convince a patient in remission of the necessity of operation. It is certain, however, that there comes a time, earlier than has frequently been the case in the past, when it is desirable to tell such a patient that he has exhausted the possibilities of nonoperative management and that to continue to go through recurring acute episodes of ulcer activity is to increase the risk of the operative procedure when it is eventually carried out. How many attacks of recurrent ulcer activity a patient should be permitted to undergo cannot be definitely stated, but it is certain that it is definitely unwise to let five, ten and fifteen years of recurrent duodenal-ulcer activity pass, as is now so frequently the case.

TABLE 2. *Mortality Following Resection for Ulcer, 1946–1950.*

	No. of Patients	No. of Deaths	Mortality %
Duodenal ulcer	660	17	2.57
Gastric ulcer	221	7	3.1
Jejunal ulcer	69	3	4.3
Gastrojejunocolic fistula	28	3	10.7

We are aware, in making this suggestion, that there will be great difficulty in bringing about much change. We wish to demonstrate that it can be done, however, by stating that such an attitude has been successfully attained in the co-operative management of these cases in our own gastroenterologic and surgical groups. We believe that if we can make the physician or gastroenterologist in charge of the nonsurgical management of these patients more acutely aware of the fact that delay when such measures fail adds definitely to the mortality of the operative procedures, we may be able to persuade physicians to recommend earlier operation for those patients with duodenal ulcers that have failed to heal under medical management (Table 2).

Banthine

One of the newest drugs employed in the nonoperative treatment of peptic ulcer is Banthine. Its effect, through its anticholinergic action, is similar to that of atropine. It decreases gastric motility, delays gastric emptying time and diminishes peristalsis in the small bowel and colon. It usually abolishes free gastric acid, and the total volume of gastric secretion is usually decreased.

McDonough and O'Neil,[1] of this clinic, have recently reported before the American Gastroenterological Association the results of the use of this drug in 100 patients with duodenal ulcer. These 100 were selected from among patients who had been under conventional ulcer management and had established the periodicity of their symptoms and in whom it could be anticipated, from their past histories, that recurrence of their ulcer attacks could be fairly well predicted. Of this group, 59 patients were relieved of symptoms and did not develop the recurrence that on the basis of the past history would have been expected. Eleven were unable to tolerate the drug because of side-reactions; 30 developed recurrence of ulcer symptoms while taking the drug. Of those with recurrence of symptoms, 7 had partial gastrectomy after failure to be relieved by the drug, 1 underwent posterior gastroenterostomy with vagotomy because of failure of the drug, 4 others have been advised to have operation and 8 are continuing under medical management without Banthine.

McDonough and O'Neil believe that Banthine is a useful addition to the medical management of duodenal ulcer but will not prevent the development of complications that require surgical procedures. They do not agree with some of the recently published enthusiastic reports that Banthine is so effective that it can be used alone in the treatment of duodenal ulcer with no need of surgery.

Hemorrhages

The problem of when to operate on a patient with massive hemorrhage from duodenal or gastric ulcer has interested everyone dealing with these cases. Many papers have been written on the subject; as a result of our own experience and of reading these reports, we wish that we could present a plan whereby one could say that by following a given formula surgery should be performed at specific times in patients with such bleeding ulcers. The decision for or against operation in bleeding peptic ulcers is not an easy one, in spite of the fact that the mortality from hemorrhage in bleeding ulcers is real. Lewison,[2] in a study of a collected series of 3499 cases, found a mortality rate of 4.3 per cent in those treated medically and of 19.5 per cent in 460 cases (collected series also) treated surgically. Bleeding ceases spontaneously, and the patients recover in so many such cases that the problems of how

long to continue the nonoperative measures in these patients and when to operate cannot be easily summed up.

We are sure that, as in so many other surgical conditions, to wait until everyone is certain that a surgical procedure should be performed on patients with bleeding peptic ulcers is to create a mortality rate that is almost prohibitive. It is a decision that must be made fairly early, particularly in those patients who present recurring massive hemorrhages. As we have dealt with these patients with hemorrhage from a bleeding ulcer, the obtaining by the physician of an early surgical consultation concerning the need of operation would prevent many of these bleeding patients from coming to surgery as late as is often the case.

Perhaps the most factual statement concerning indications for immediate operation on patients with bleeding peptic ulcer is that surgical measures to control bleeding should be instituted when the total blood volume drops below 60 per cent.

We are sure, from our own experience with this problem, that no patient who has bled seriously is

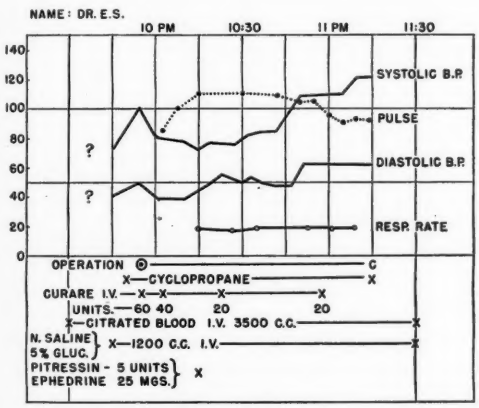


FIGURE 1. *Anesthesia Chart of Operation to Control Massive Hemorrhage from Duodenal Ulcer.*

The blood pressure could not be recorded before anesthesia was started. The initial anesthetic agent for laparotomy was cyclopropane. Note that curare was given later to obtain relaxation. Note improvement of the blood pressure during operation after transfusion and drug therapy.

in too poor condition due to exsanguination to be operated on for control of the bleeding vessel[3] (Fig. 1). It has been our experience in operating on these patients, who are cold, pulseless and with no blood pressure, that when the bleeding vessel has been controlled and the vascular system has been replenished by transfusion, they regain normal pressure and leave the operating table in surprisingly good condition.

Recurring Pyloric Obstruction

A most troublesome decision for or against surgery has concerned the patient with recurring pyloric obstruction. In these patients the plan employed and proposed by Wilkinson,[4] of this clinic, of introducing a 3-ounce noncurding milk mixture every hour through an indwelling gastric tube, clamping the tube for the first half hour and draining it for the second half hour throughout the twenty-four hours

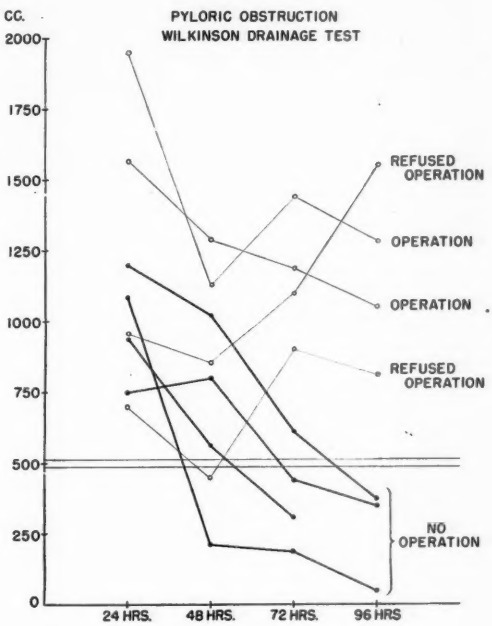


FIGURE 2.

for three to four days and determining the changes in the amount of residual material has helped us to make this decision early. We have also been encouraged to carry out positive operative procedures in patients with recurring or persisting pyloric obstruction when this condition has existed for three months or more (Fig. 2). In a group of 100 patients who had had such an obstruction less than three months, surgery was indicated in 39 per cent of the cases, whereas in those patients who had had such recurring attacks for over three months surgery was necessary in 69 per cent of the cases.

Malignancy in Gastric Ulcer

One of the most serious problems in gastric ulcer is the difficulty in differentiating a malignant ulcer and a benign ulcer. The literature is replete with reports on the problem, with the internist often advising long periods of medical man-

agement for this dangerous lesion. Smith and Jordan[5] of our clinic reported on a group of 600 patients, 270 of whom were operated on; in this group cancer was found in 59, or 21.8 per cent. In a previous communication by Marshall and Welch[6] of the clinic on a study of 131 surgical cases in which the preoperative diagnosis was benign ulcer, 26 (19.6 per cent) gastric carcinomas were found. It is generally conceded that the rate of diagnostic error in this condition consistently ranges from 10 to 20 per cent. The size of the ulcer, its site of origin, the age of the patient and the amount of gastric acids present give little dependable information concerning the presence or absence of malignancy in such ulcers. It can be said quite safely, however, that nearly every ulcer arising on the greater curvature of the stomach is malignant. In our entire experience with gastric surgery, we have seen only 5 benign ulcers of the greater curvature (Fig. 3 and 4).

FIGURE 3. *Roentgenogram of 72-Year-Old Man, Showing Ulcer of Greater Curvature of Stomach.*
Arrows indicate location of ulcer on greater curvature.
Inset = lateral view, showing penetration of gastric wall. Preoperative diagnosis was carcinoma; pathological examination revealed benign ulcer (see Fig. 4).

Over the years during which 356 patients have been operated on for gastric ulcers, the number has progressively increased year by year. In the last five years we have performed partial resection on 221 patients with gastric ulcer, whereas in the fifteen years prior to this period resection was carried out in only 121 cases. Approximately 1 out of any 3 patients with gastric ulcers seen in this clinic over this five-year period has come to operation.

We agree with Dr. Jordan of the clinic's Department of Gastroenterology that a patient with a gastric ulcer, a lesion with a great potentiality for malignancy, may be treated medically in the hospital until complete healing (Fig. 5) is or is not obtained, but if there is failure of the lesion to heal completely within six weeks that patient should be treated as soon as possible by gastric resection.

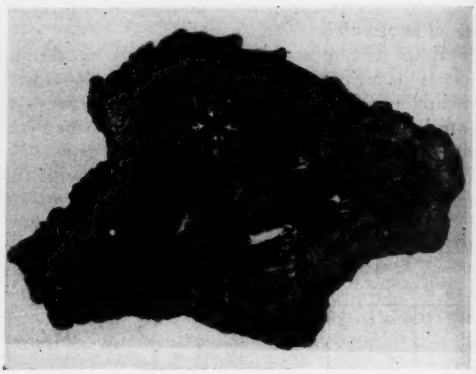


FIGURE 4. *Resected Specimen of Benign Gastric Ulcer on Greater Curvature of Stomach (Shown in Fig. 3).*

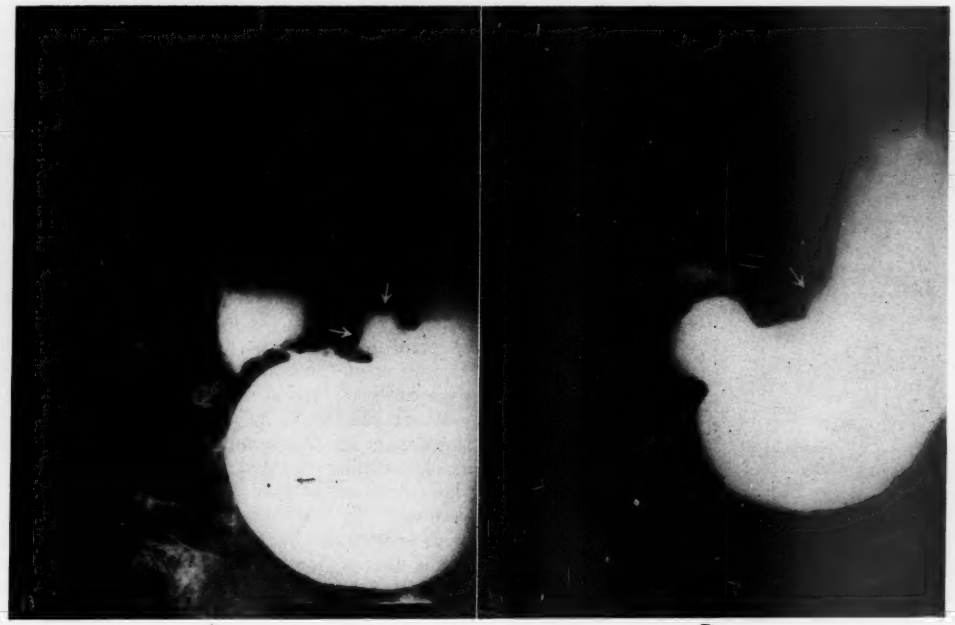
All recurrent gastric ulcers should be promptly treated by resection, the patient's condition permitting.

The physician who undertakes nonsurgical management of a patient with gastric ulcer is faced with a serious responsibility. He must be certain that such patients are rechecked at least every two months for a minimum of six months. In view of the accepted evidence of malignancy in 10 to 20 per cent of all cases of gastric ulcer, no other plan will satisfactorily discover diagnostic error at an early enough date to avoid unjustifiable delay in radical measures (Fig. 6).

It is to be remembered that such patients under a medical regimen and enjoying the consequent gastric comfort will usually neglect such early and frequent check-up examinations, and the need for pressure on them will be great.

The presence of a gastric ulcer high on the lesser curvature has always presented a difficult problem to the surgeon because of its location and because if the ulcer is large and extensive it may well require total gastrectomy for its removal. Such cases are few in number; most ulcers on the lesser curvature will be at such a level that partial gastrectomy can be performed and total gastrectomy will not

be required. We have had 13 patients, however, on whom total gastrectomy (Fig. 7) was carried out for benign ulcerating lesions of the stomach (Table 3). A good follow-up is now available in 12 of these cases; Table 3 shows that excellent results were obtained in all 12 cases. The only death in the 13 cases occurred in a patient with an ulcer that had perforated and on whom total gastrectomy was performed as an emergency measure. The reasons for total gastrectomy in each case are also given in this table.



A B

FIGURE 5. *Roentgenograms of Large Gastric Ulcer of the Lesser Curvature.*
A = *Taken February 23, 1945; medical and dietary therapy were instituted in hospital.* B = *Taken March 23, 1945. The lesion was almost healed; the patient was asymptomatic and was discharged without operation. Repeated roentgenologic examinations have shown that healing has been maintained.*

DUMPING SYNDROME

One objection to partial gastrectomy for peptic ulcer has been the occurrence of the dumping syndrome. This syndrome is consistently associated with food intake and in most instances occurs during or shortly after a meal. It is associated with nausea, occasionally with vomiting, frequently with weakness and sometimes with palpitation, pallor and sweating.

The incidence of this complication as noted in various reports has varied greatly from that of Muir,[7] who reports 75 per cent in 124 cases, to that of Kennedy, Reynolds and Cantor[8] of only 1.3 per cent in 75 cases.

We have always been impressed by the fact that the dumping syndrome has been a complication of partial gastrectomy that has bothered us very little. To test this impression, Camblos and Lahey[9] recently investigated 100 consecutive cases of partial gastrectomy performed within the last year, to ascertain the incidence of this distressing condition. Ninety of the 100 cases could be accurately followed; of these only 2 patients reported any symptoms suggestive of the dumping syndrome, and in 1 these symptoms disappeared during the period of correspondence.

The theories concerning the origin of this condition have been based largely on two presumptions: that it is a mechanical distention of the jejunal loop and that it is the result of a chemical factor based on the premise that there is an abnormally rapid delivery of undiluted hypertonic fluid into the jejunum, which is followed by rapid absorption of sugar, evidenced by a compensatory rise in blood sugar to a high level, and then by a precipitous fall to a hypoglycemic level. Adherents to this theory have ascribed the symptoms described above to this immediate hyperglycemic phase, followed in some hours by a hypoglycemic phase.

Since we have been bothered so little by this complication and since we have so consistently employed one type of partial gastrectomy in approximately 1600 such cases, we believe that the type of operation employed has played an important part in its avoidance.

The type of gastric resection and gastrojejunal anastomosis shown in Figure 8 has, in our opinion, had at least something to do with the very limited occurrence of this complication in our experience.

FIGURE 6. *Ulcer of Lesser Curvature of Stomach in a 38-Year-Old Man.*

The patient had been treated medically in hospital for eighteen days with symptomatic improvement but no roentgenologic change in ulcer. Gastric resection was performed; the pathological report was carcinoma simplex.

The Hofmeister type of anastomosis, with buttressing of the distal jejunal loop over the closed upper two thirds of the stomach and anchoring of the uppermost stitch to the ligature of the gastrohepatic omentum, produces an angulation, as shown, which in some measure acts as a trap and, as demonstrated by postoperative roentgenograms, by virtue of its traplike nature prevents rapid dumping of gastric contents and mechanical overdilatation of the anastomosed jejunal loop. It is to be observed in this type of anastomosis that the proximal loop has been routinely anastomosed to the greater curvature and that the angulation is produced at the last suture of the distal loop to the closed end of the stomach by the ligature described above. Another factor that may be concerned with the avoidance of this complication is the employment of a small gastrojejunal stoma, two fingerbreadths in diameter.

Pancreatitis

As stated previously, the mortality in partial gastrectomy, — particularly in duodenal ulcer, — is largely related to removal of the indurated ulcers from the head of the pancreas, particularly when this is done by surgeons unfamiliar with the procedure. A possible serious complication of this operation is pancreatitis, particularly in the head of the pancreas. Warren,[10] of this clinic, has recently reported our experiences with pancreatic injuries following partial gastrectomy.

Everyone who has had any considerable experience with partial gastrectomy for duodenal ulcer has been made acutely aware of the hazards of pancreatitis following resection of these ulcers and removal of such ulcers from the head of the pancreas. They have likewise seen such pancreatitis develop when the removal of the duodenal ulcer in no way involved the head of the pancreas; such pancreatitis has also occurred in patients in whom no freeing of the duodenum from the head of the pancreas was carried out.

We should like to make two warnings concerning the danger of this complication in patients with duodenal ulcer treated by partial gastrectomy. One relates to the need of inspecting the duodenum very carefully whenever it is peeled out of the head of the pancreas. Because of the superficial position of the duct of Santorini, entering as it usually does through a separate opening into the duodenum, this structure should be carefully searched for as the duodenum is removed from the head of the pancreas as it occasionally must be, in order to obtain an adequate length to invert safely; if seen, it must be securely ligated with cotton or silk. The other warning with regard to increasing the hazard of pancreatitis in closing duodenal stumps concerns the avoidance of the introduction of needles or sutures into the head of the pancreas, lacerating pancreatic ducts, constricting blood supply and thus promoting the possibility of this undesirable complication.

Pancreatitis of itself, limited to the head of the pancreas, would not be of such great seriousness; its serious consequences are due to the fact that it frequently results in digestion of the suture material, edema, swelling and necrosis of the inverted duodenum and the production of duodenal leakage.

Vagotomy

In surgical treatment of peptic ulcer probably nothing has created more heated discussions and even direct conflict of opinion than the position of vagotomy in the treatment of duodenal and gastrojejunal ulcer. We have not enthusiastically sup-

ported a surgical program that puts vagotomy in first position in the treatment of duodenal and jejunal ulcer. During the understandably vigorous promotion of this relatively new surgical procedure, we have preferred to employ the operation ourselves in a selected group of 78 cases in order to observe its results and to delay our final conclusion concerning its place until it had become a more seasoned procedure and until more data were available by which it could be evaluated in terms of benefit and complications. These data are now at hand.

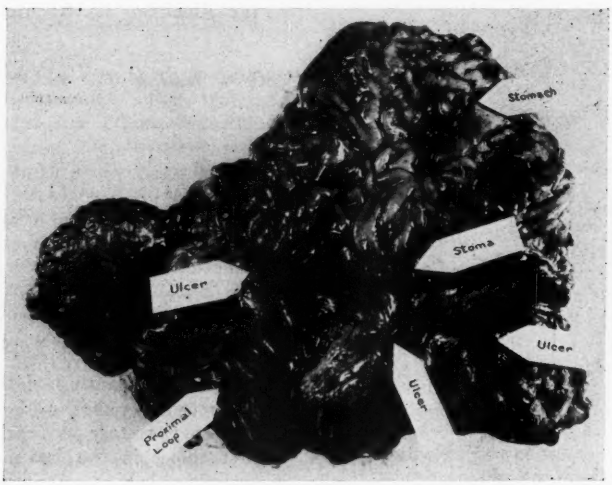


FIGURE 7. *Resected Specimen of Gastrojejunostomy with Multiple Recurrent Ulcers (Case 7, Table 3).*

We believe that one of the most logical approaches to determining when vagotomy should be performed and its relation to partial gastrectomy was proposed by Phemister[11] a year and a half ago in a discussion of this subject at a meeting of the American Surgical Association. He suggested that there were three phases of the control of hyperacidity that, particularly in duodenal ulcer and gastrojejunal ulcer, are basically related to the origin and persistence of symptoms in these lesions: the cephalic phase, controllable by vagotomy; the gastric phase, controllable through lowering gastric acidity to or below 10 by high partial gastrectomy; and the intestinal phase, probably not satisfactorily controllable by any means. He stated that if a patient had had an adequate partial gastrectomy (removal of 70 per cent or more of the stomach), another resection in such a patient was futile, as the possibility of control of gastric acidity by means of partial gastrectomy had already been exhausted

TABLE 3. *Indications for Total Gastrectomy.*

Case No.	Patient	Indications	Result	No. of Years Since Operation
1	G. K.	Carcinoma suspected	Excellent	8
2	J. L.	High lesser-curvature ulcer; carcinoma suspected	Excellent	6
3	I. S.	2 high lesser-curvature ulcers	Excellent	5½
4	T. F. F.	High cardia ulcer; perforation into liver	Excellent	4½
5	J. H. P.	High lesser-curvature ulcer	Excellent	4¼
6	M. M.	High lesser-curvature ulcer	Excellent	4¼
7	P. M.	Subtotal resection for duodenal ulcer 1940; re-resection for jejunal ulcer 1942; transthoracic vagotomy 1946; total resection for jejunal ulcer 1948	Excellent	3¼
8	C. D. C.	High greater-curvature ulcer; perforation into spleen; explored 6 weeks previously elsewhere; referred for total gastrectomy	Excellent	3
9	A. B.	Lesser-curvature ulcer 4 cm. from esophagus	Excellent	3
10	E. P.	High lesser-curvature ulcer	Excellent	2½
11	L. L.	Active gastric ulcer at esophagus with hemorrhage	Excellent	2
12	M. C.	High lesser-curvature ulcer; perforation into pancreas; carcinoma suspected	Excellent	2
13	H. F.	3 gastric ulcers of lesser curvature (1 with perforation); performed as emergency operation	Dead	—

by the adequate partial gastrectomy and that if in such a case further surgery was anticipated vagotomy to inhibit the cephalic phase was then the logical approach to this problem.

This is the position that we had taken since the time when interest in vagotomy was first reacti-

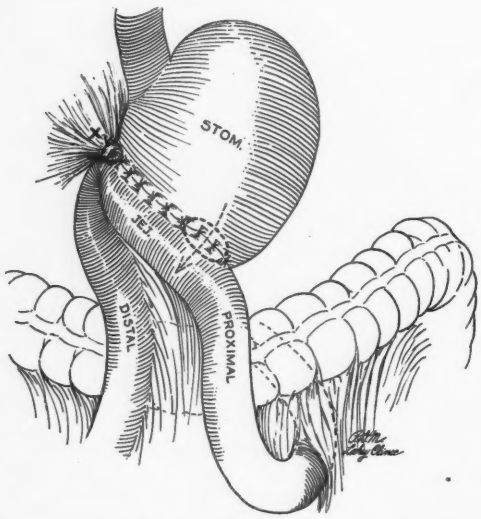


FIGURE 8. *Technic of Gastric Resection and Gastrojejunal Anastomosis Employed at the Lahey Clinic.*

vated by Dragstedt.[12] We have maintained this position through recent years in our management of peptic ulcers and in our statements concerning our attitude toward the place of vagotomy in the

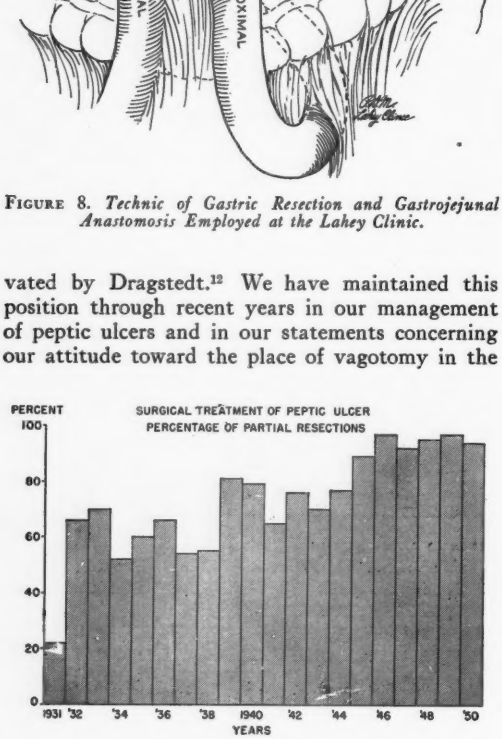


FIGURE 9.

surgical management of duodenal and jejunal ulcer. We have maintained that partial gastrectomy, until other operations are proved better, must occupy first place in the selection of any operative procedure for a patient with duodenal, jejunal or gastric ulcer (Fig. 9).

Enough cases have now been treated and enough time has now elapsed, and the recent vagotomy study of the American Gastroenterological Association's Committee for the Study of Peptic Ulcer[13] has now made available enough data from which conclusions can be drawn that it can be determined whether or not this has been a sound position.

The recent report by the Vagotomy Committee of the American Gastroenterological Association,

TABLE 4. *Duodenal-Ulcer Patients Clinically Free of Ulcer Symptoms.**

CONDITION	PERCENTAGE OF PATIENTS
No previous hemorrhage	
Gastric resection	95.6
Gastric resection and vagotomy	96.8
Gastroenterostomy and vagotomy	71.7
Previous hemorrhage	
Gastric resection	96.4
Gastric resection and vagotomy	96.1
Gastroenterostomy and vagotomy	83.8

*Adapted from Jordan, S. M.[13]

under the chairmanship of Dr. Sara M. Jordan,[13] in the recently published book *Peptic Ulcer* now provides satisfactory evidence that the operation of first choice in the treatment of duodenal and jejunal ulcers is high gastric resection, with or without vagotomy. In the tables reproduced from this recent article by Dr. Jordan, it will be seen that it makes very little difference in the end results in those patients with these lesions, with or without a past history of hemorrhage, whether or not a vagotomy is added to the partial gastrectomy

TABLE 5. *Incidence of Hemorrhages Reported in Follow-up Study of Duodenal Ulcer.**

CONDITION	NO. OF CASES	PERCENTAGE OF CASES
No previous hemorrhage		
Gastric resection		
Less than 70 per cent resection	395	6.3
More than 70 per cent resection	455	1.3
Total of all resections	850	4.3
Gastric resection and vagotomy	224	1.3
Gastroenterostomy and vagotomy	872	2.1
Previous hemorrhage		
Gastric resection		
Less than 70 per cent resection	139	10.7
More than 70 per cent resection	47	4.2
Total of all resections	186	8.6
Gastric resection and vagotomy	138	4.3
Gastroenterostomy and vagotomy	306	6.5

*Adapted from Jordan, S. M.[13]

(Table 4). Whether or not the partial gastrectomy is of the type designed to remove 70 per cent or more of the stomach is extremely important as regards the end results. This is strikingly demonstrated in Table 5, which deals with the incidence of recurrent hemorrhage after partial gastrectomies in which less than 70 per cent and more than 70 per cent of the stomach was removed.

Vagotomy alone, with its frequent necessity for secondary drainage operations necessitated by resulting gastric retention, has today largely been abandoned. It is to be noted in Table 4 that with gastroenterostomy, the operation now most commonly employed in connection with vagotomy, the percentage of patients with duodenal ulcer who are clinically free from ulcer symptoms is distinctly less than that obtained with gastric resection, with or without vagotomy.

So much has been said concerning the high place of vagotomy in the treatment of gastrojejunal ulcer that Table 6 is of distinct interest. In this table the results of gastric resection alone are compared with the results of vagotomy alone. Our belief that partial gastrectomy in the treatment of gastrojejunal ulcer was to be preferred to vagotomy has been borne out by the figures in Table 6.

It is the opinion of this committee, from data based on the study of 2441 cases of duodenal ulcer and 323 cases of jejunal ulcer, of which 1300 duodenal ulcers and 166 gastrojejunal ulcers have been studied between two and a half and three years, that it can be stated that the addition of vagotomy to gastric resection has not improved the results of this operation, even in patients with histories of bleeding. This agrees with our own findings of some two years ago in a group of 50 cases in which partial gastrectomy with vagotomy (25 cases) and without vagotomy (25 cases) was compared. It can also be stated that partial gastrectomy still occupies the first position in the treatment of duodenal and gastrojejunal ulcer.

Data are not yet available to permit conclusive statements concerning the incidence of complications of vagotomy. It has been stated by those who have reviewed these data (reports of the complications will be published later) that the percentages of patients having had abdominal distress, diarrhea and variations in weight are high enough to constitute a real objection to the employment of vagotomy in the treatment of duodenal and jejunal ulcer except when all other measures have been exhausted.

Summary

Earlier partial gastrectomy in ulcer patients under medical management is urged for the further lowering of the mortality rate in partial gastrectomy for duodenal ulcer.

The problem of deciding for or against surgery in the patient with a bleeding ulcer is discussed.

The development of pancreatitis after partial gastrectomy is discussed, and measures to decrease the incidence of this condition are considered.

A plan for deciding for or against operation in patients with recurring pyloric obstruction is presented.

The relation of cancer to gastric ulcer is considered.

The position of vagotomy in the surgical treatment of duodenal and jejunal ulcer is discussed.

Table 6. *Gastrojejunal Ulcer: Results According to Combined Criteria.**

Condition	Percentage of Cases
No previous hemorrhage	
Vagotomy alone	59.1
Gastric resection alone	81.4
Previous hemorrhage	
Vagotomy alone	61.6
Gastric resection alone	86.1

*Adapted from Jordan, S. M.[13]

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REVERSIBLE TOXIC MANIFESTATIONS IN PATIENTS WITH CIRRHOSIS OF THE LIVER GIVEN CATION-EXCHANGE RESINS*

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SEVERAL reports attesting to the efficacy of cation-exchange resins as therapeutic adjuncts in the management of congestive cardiac failure[1-9] suggest their use in other clinical states associated with fluid retention. The resins are not absorbed from the gastrointestinal tract; when taken by mouth they act by binding sodium, thus preventing its absorption and resulting in excretion of the bound sodium in the stool.[1, 3, 10] As sodium is bound, other cations, — for example, NH_3+ or $H+$, — are released and are presumably available for absorption. Clinical evidence of toxicity has been meager, with the exception of the development of hypokalemia in some cases. This hazard has been reduced recently[4, 6] by the use of resin that contains potassium and therefore provides this ion for absorption.

It is well established that diets rigidly restricted in sodium content are effective in controlling and preventing ascites and edema formation in patients with cirrhosis of the liver.[11-13] The difficulties encountered in maintaining this diet in some patients justified a therapeutic trial of cation-exchange resins. Accordingly, 12 patients with ascites and edema due to cirrhosis of the liver were treated with resins. The clinical and laboratory observations, which are reported here, indicate that although a diuresis frequently occurs many patients receiving resins containing ammonium develop neurologic manifestations resembling those of impending hepatic coma.

TABLE 1. *Clinical and Laboratory Data on 12 Patients with Cirrhosis of the Liver.*

Patient	Age	Sex	Ascites	Edema	Size of Liver	Size of Spleen	Icteric Index	Urinary Bile	Urine Urobilinogen	Serum Albumin	Thymol Turbidity	Thymol Flocculation	Cephalin Flocculation	Prothrombin Concentration	Bromsulfalein Retention
					cm. below costal margin	*cm. below costal margin*			*dilution*	*gm./100 cc.*	*cc. $BaSO_4$**	*24hr.*	*48hr.*	%	%
J. L.	57	M	++++	++	Not palpable	Not palpable	8	0	1:32	2.9	–	–	+++	80	22
H. M.	57	M	++++	++++	6	Not palpable	20	+	1:32	3.0	3.2	+++	–	53	16
A. R.	43	F	+++	0	8	Not palpable	5	0	1:16	1.9	2.8	0	–	70	8
R. E.	48	M	++++	+++	5	2	30	++	1:1024	2.0	–	–	++++	44	40
M. S.	35	F	++++	++	7	3	60	+++	1:116	1.8	–	–	+++	48	–
N. B.	33	F	++++	++++	7	6	50	++++	1:512	2.8	–	–	+++	30	–
J. G.	46	M	+++	+	4	Not palpable	20	0	1:64	2.0	2.5	0	–	36	42
J. C.	52	F	++++	0	6	Not palpable	10	0	1:128	–	–	–	–	–	32
H. H.	43	F	++++	+	5	Not palpable	7	0	1:64	4.2	1.0	0	–	–	47
R. P.	50	M	++++	++	2	1	35	+	1:256	3.7	5.5	+++	–	38	48
A. B.	50	F	++++	++	7	Not palpable	90	++++	1:128	2.3	5.7	+++	++++	47	–
M. H.	65	F	++++	+	7	5	100	++++	1:128	2.4	3.2	0	++++	65	–

*Normal value <1.7 cc. $BaSO_4$ suspension.

MATERIAL AND METHODS

The clinical and laboratory findings on the 12 patients studied are shown in Table 1. All patients had histories of chronic alcoholism and displayed evidence of severe hepatic cirrhosis with ascites. None had complicating or coexisting heart or kidney disease as judged by the usual clinical and laboratory criteria. The patients were followed on the medical wards of the Boston City Hospital, except J. G. and J. C., who were studied as out-patients. Body weights were usually measured daily and the amount of ascites and edema estimated. Changes in body weight were considered indices of fluid balance, since accurate measurements of the intakes and outputs of electrolytes and water were not possible under the conditions of the study. Serum sodium and potassium concentrations were measured by the internal standard method of flame

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photometry,[14, 15] serum chloride by the method of Schales and Schales[16] and serum carbon-dioxide content by the Van Slyke method.[17] In a few patients serum calcium concentration was also determined.[18]

Laboratory tests made to assess liver function included the icteric index, urinary bilirubin,[19] urinary urobilinogen,[20] serum albumin concentration,[21] thymol turbidity[22, 23] and flocculation, cephalin cholesterol flocculation,[24] plasma prothrombin concentration[25] and bromsulfalein retention (5 mg. per kg. of body weight at forty-five minutes).[26]

The period of resin therapy in each patient was preceded by a control period to ensure that ascites and edema were either stable or increasing. Four patients were given an ammonium exchange resin* in doses of 60 to 90 gm. daily for from three to thirteen days; 4 patients were given a hydrogen exchange resin† in doses of 45 to 80 gm. daily for from nine to twelve days; 4 additional patients were given an ammonium-potassium exchange resin† in doses of 30 to 90 gm. daily for from three to twelve days. The resins were taken orally in divided doses as aqueous suspensions after meals. The patients were followed for from two to seventeen days after cessation of resin therapy. No alterations in the basal therapeutic regimens of these patients were made after the institution of the studies. The patients received no diuretics other than the resin. When untoward reactions to the resins were observed no attempt at treatment was made, except to stop resin administration. However, those patients who developed significant hypokalemia were given intravenous injections of fluids containing potassium as soon as such a diagnosis was established.

During 9 of the 18 courses of resin therapy studied, a diet containing 200 mg. of sodium was provided; during the other 9 therapeutic trials the regular hospital diet was employed.

Results

Ammonium Cation-Exchange Resin (Table 2)

Therapeutic effect. Four patients (H. M., J. L., A. R. and R. E.) with cirrhosis of the liver and ascites were observed clinically during 8 courses of therapy with an ammonium exchange resin. During each course the resin was administered orally in doses of 20 to 30 gm. three times daily for three to thirteen days (total doses, 140 to 900 gm.). In all cases diuresis occurred, resulting in losses of from 6.5 to 23 pounds of body weight and clinically evident decreases in ascites and edema. In several cases fluid retention ocurred after the withdrawal of resin.

Untoward effects. Alterations in mental status occurred in 3 of the 4 patients. For example, H. M. became disoriented and confused after receiving 180 gm. of resin in three days. These symptoms increased for two days, at which time resin administration was stopped. By this time the patient had become irrational at night and displayed inappropriate behavior, such as stuffing newspaper into the toilet bowl and urinating in the water pitcher. At times he seemed to have insight into his mental status, realizing that he was "mixed up." Clearing of this confusion took place gradually in the four days following cessation of resin therapy. Because of the similarity of this episode to a previous three-day period of disorientation that had occurred spontaneously about three weeks prior to the start of resin therapy, it was reinstituted to determine whether or not the psychosis could be precipitated again. After nine days of resin (540 gm.) the patient appeared drowsy, his speech was slurred and he said that he was becoming "mixed up." This was followed shortly by confusion, disorientation, incoherent mumbling and aimless wandering about the ward. Resin was discontinued; in four days the patient's mental status was essentially normal and continued so during an additional month of observation.

Patient J. L. showed no serious untoward reactions during his first course of resin therapy (nine days, 540 gm.). On the thirteenth or last day of his second course of resin (900 gm.) he appeared drowsy, listless and apathetic, in contrast to his usual euphoric personality. His speech was thick and slurred, and he was disoriented with regard to time and place. The only other neurologic findings at this time consisted of a coarse irregular tremor of the outstretched hands that became flapping in quality as posture was sustained. This could be elicited in the fingers, wrists, elbows, legs and facial muscles. In one day after cessation of resin administration the patient's mental status was normal, and in two days the tremor was no longer present. A third course of resin given for eleven days (720 gm.) to this patient failed to precipitate these neurologic manifestations.

After receiving 140 gm. of resin in three days, R. E., whose mental status was previously normal, developed a tremor similar to that noted above, became disoriented and confused and displayed inappropriate behavior. This was followed by a period of agitation, during which the patient had to be restrained. In one day after the resin was discontinued the mental disturbance cleared, and after two days the tremor had vanished.

Two eight-day courses of resin (total doses, 600 and 720 gm.) were given to A. R., who maintained a normal neurologic status throughout.

Other incidental untoward effects attributable to the administration of this resin were constipation in 3, fecal impaction in 1 and anorexia in 1. Two patients also complained of cramps in the legs on the last day of resin administration.

*The ammonium cation-exchange resin (Win 3000) was generously provided by Winthrop-Stearns, Incorporated, of New York.

†The hydrogen cation-exchange resin (SKF No. 741) and the ammonium-potassium cation-exchange resin (Resodec) were generously provided by Smith, Kline and French Laboratories, of Philadelphia.

Hydrogen Cation-Exchange Resin

Therapeutic effect. Four patients (M. S., N. B., J. G. and J. C.) were given a hydrogen cation-exchange resin in doses of 45 to 80 gm. daily for nine to twelve days. Diureses with body-weight losses of from 11 to 40.5 pounds occurred on four occasions in 3 of the patients. A diuresis did not occur in the fourth patient.

Untoward effects. Marked hypokalemia occurred in 2 patients (J. G. and J. C.). These patients were admitted to the hospital after twelve and nine days of resin therapy, respectively. J. G. appeared drowsy and had marked generalized weakness with hyporeflexia, but was rational, responsive, co-operative and oriented in all spheres. Tremor was not present. His serum-potassium concentration shortly after hospital admission was 2.1 milliequiv. per liter, and an electrocardiogram showed changes consistent with hypokalemia. Intravenous administration of potassium was instituted, but the patient died of massive bleeding from esophageal varices within twenty-four hours of hospital entry.

J. C. was admitted to the hospital in coma. Her breathing was Kussmaul in type, and she responded only to noxious stimuli. She was atonic, and deep tendon reflexes were markedly depressed. The serum-potassium concentration immediately after hospital entry was 1.5 milliequiv. per liter, and an electrocardiogram confirmed the hypokalemia. The patient was given potassium chloride intravenously during the first twenty-four hours and then by stomach tube for twenty-four hours. After this her serum-potassium concentration rose to 3.6 milliequiv. per liter; she spoke coherently, appeared oriented and was able to eat. After seventy-two hours she appeared normal in all respects except for generalized weakness. No tremor was evident at any time.

TABLE 2. *Clinical and Laboratory Data on Patients with Cirrhosis of the Liver and Ascites Treated with Cation-Exchange Resins.*

Patient	Dates of Study	Dates of Therapy	Period of Resin Therapy	Daily Dose of Resin	Total Dose of Resin	Diet	Body Weight				Ascites		Edema	
							First day of study	First day of resin	First day after resin	Last day of study	Before resin	After resin	Before resin	After resin
			days	*gm.*	*gm.*		*lb.*	*lb.*	*lb.*	*lb.*				
H. M.*	6/18–7/13	6/21–6/25	5	60	260	Low sodium	233.0	226.0	216.3	220.3	4+	3+	4+	2+
	6/26–8/7	7/13–7/21	9	60	540	Low sodium	216.3	220.3	208.3	215.0	3+	1+	2+	1+
J. L.*	7/1–7/19	7/4–7/12	9	60	540	Ward	137.0	138.5	115.5	128.0	4+	1+	2+	0
	7/13–8/8	7/20–8/1	13	40–60	900	Ward	115.5	128.0	110.5	120.5	3+	0	1+	0
	8/1–8/20	8/9–8/19	11	40–60	720	Ward	110.5	120.5	109.8	—	1+	0	±	0
A. R.*	8/16–9/12	8/20–8/27	8	40–60	600	Low sodium	133.3	134.8	125.8	134.0	4+	2+	1+	0
	8/27–10/8	9/13–9/21	8	90	720	Low sodium	125.8	134.0	123.5	129.0	4+	2+	0	0
R. E.*	7/31–8/9	8/4–8/6	3	60	140	Ward	155.0	157.5	150.5	153.0	3+	3+	3+	2+
M. S.†	4/24–5/19	4/29–5/9	11	60	660	Ward	131.0	142.5	119.0	112.0	4+	1+	4+	±
N. B.†	5/4–5/29	5/14–5/25	12	60–80	860	Ward	200.0	212.5	172.0	176.3	4+	2+	4+	2+
	5/26–6/18	5/29–6/9	12	80	960	Ward	172.0	176.3	158.0	158.0	3+	±	2+	1+
J. G.†	4/28–5/19	5/6–5/18	12	45–75	615	Low sodium	195.0	195.0	194.0	—	3+	3+	1+	1+
J. C.†	4/29–5/19	5/5–5/13	9	45	405	Low sodium	106.0	107.3	96.3	—	4+	2+	0	0
H. H.‡	3/25–4/17	4/4–4/13	10	30–90	600	Low sodium	156.0	157.5	146.5	147.8	4+	3+	1+	1+
R. P.‡	4/29–5/16	5/9–5/12	4	30–60	210	Low sodium	154.0	154.3	150.0	152.5	4+	4+	2+	2+
	5/13–5/20	5/16–5/18	3	30–60	150	Low sodium	150.0	152.5	150.0	150.3	4+	4+	2+	2+
A. B.‡	7/14–8/3	7/17–7/28	12	30–45	450	Ward	218.0	223.3	202.0	210.5	4+	3+	2+	1+
M. H.‡	7/13–8/2	7/17–7/25	9	30–60	375	Ward	128.0	130.8	117.5	123.8	4+	2+	1+	1+

*Ammonium cation-exchange resin.
†Hydrogen cation-exchange resin.
‡Ammonium-potassium cation-exchange resin.

A third patient (N. B.) received two courses of resin therapy without untoward effect and with only modest reductions in the serum-potassium concentration. Resin therapy was finally discontinued because of an interceding episode of massive gastrointestinal bleeding, possibly due to ruptured esophageal varices. M. S., the fourth patient studied, had an entirely asymptomatic course, with no alteration in serum potassium concentration.

to 600 gm.). Three patients (H. H., A. B. and M. H.) showed decreases in ascites and edema, with body-weight losses of from 11 to 21 pounds. The fourth patient, R. P., lost small amounts of body weight during two separate but short courses of resin. Longer periods of resin administration were not possible in this patient because of the development of the complications described below.

Untoward effects. The untoward effects noted in this group of patients were similar to those observed

TABLE 2 (*Concluded*).

PATIENT	SERUM ELECTROLYTES															DIURESIS	UNTOWARD REACTIONS
	SODIUM			POTASSIUM			CARBON DIOXIDE			CHLORIDE			CALCIUM				
	Control	Last Day of Resin	3–7 Days After Resin	Control	Last Day of Resin	3–7 Days After Resin	Control	Last Day of Resin	3–7 Days After Resin	Control	Last Day of Resin	3–7 Days After Resin	Control	Last Day of Resin	3–7 Days After Resin		
	milli-equiv./liter	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*mM/liter*	*mM/liter*	*mM/liter*	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		
H. M.*	135.8	142.0	141.0	5.0	3.7	4.8				102	112	106				Good	Disorientation, confusion, inappropriate behavior
	139.0	137.6	139.7	4.4	3.6	4.7				98	112	108		9.0	10.1	Good	Disorientation, confusion, inappropriate behavior, slurring speech
J. L.*	142.0	138.0	134.2	5.8	5.8		29.0	20.0		123	111	92				Good	Constipation, leg cramps
		144.6	152.6					18.6	28.5	92	115	115				Good	Tremor, drowsiness, slurring speech, disorientation, constipation
		142.5	144.0		4.6	4.8										Good	None
A. R.*	140.4	141.3	142.5							110		110				Good	Leg cramps
	142.5	133.0	133.0									104				Good	Leg cramps, anorexia, fecal impaction
R. E.*		141.5			3.6			21.0			114					Fair	Tremor, disorientation, confusion, inappropriate behavior
M. S.†	137.8	140.7	140.5	4.1	4.6	4.6	20.0						8.6	8.2	8.2	Good	None
N. B.†	137.9	136.0	137.0	4.0	3.5	4.2	23.4			105			8.0	7.8	8.0	Good	None
	137.0	134.8	137.3	4.2	3.3	4.2							8.0	8.1		Good	Resin stopped because of massive gastrointestinal bleeding
J. G.†		133.0		4.8	2.1											None	Hypokalemia, fecal impaction; died of esophageal bleeding.
J. C.†		141.0	139.0		1.5	3.6		10.7	21.0		95	106				Good	Hypokalemia, acidosis, constipation
H. H.‡	133.5	132.5	144.5	4.1	4.1	4.0	26.5	12.8	17.6							Good	Drowsiness, slurring speech, epigastric distress, fecal impaction
R. P.‡	130.0	130.9	132.5	4.2	4.0	4.2	25.9	26.0			102					Poor	Mental change without frank disorientation; tremor.
	132.5	132.0	130.5	4.2	4.1	4.2	26.0	23.3			96					Poor	Mental change without frank disorientation; tremor; electroencephalographic changes.
A. B.‡	118.5	132.0	131.5	3.8	3.0	3.3		21.5	24.5	75	101	100				Good	Tremor, drowsiness, slurring speech, mild disorientation
M. H.‡	141.0	139.5	136.3	3.5	3.2	3.2	17.3	14.0	18.7	108	118	106				Good	Disorientation, confusion, delirium, tremor, drowsiness

Two of the patients in this group had constipation; one of these (J.G.), who subsequently died of massive gastrointestinal bleeding, had a fecal impaction.

Ammonium-Potassium Cation-Exchange Resin

Therapeutic effect. An ammonium-potassium cation-exchange resin was administered on five occasions to 4 patients in doses of from 30 to 90 gm. daily for from three to twelve days (total doses, 150

in the patients given the ammonium resin. That is, the primary effects noted were aberrations in neurologic status rather than the manifestations of hypokalemia and acidosis that predominated in the patients given the hydrogen exchange resin.

For example, R. P. received 210 gm. of the mixed resin in four days. On the fourth day the patient was noted to be mentally dull and apathetic and appeared to be in a daze. He laughed without ap-

parent reason. Orientation was not grossly altered, but a marked coarse, irregular, generalized, flapping tremor was apparent at rest and was severe enough to prevent co-ordinated handling of eating utensils. This tremor could be accentuated by requiring the patient to sustain a posture such as extending the arms. Neurologic examination was otherwise negative. In one day after resin administration was discontinued the patient had regained a normal mental status, and the tremor disappeared. Four days later resin in similar doses was again given; again the mental changes and tremor developed. On this occasion these abnormalities cleared after one and two days, respectively, after resin was discontinued. Serum-potassium-concentration and carbon-dioxide-content determinations and electrocardiographic tracings made before and after resin administration showed no significant alterations. However, an electroencephalogram, made when the neurologic disturbances were present, revealed bursts of high amplitude, bilaterally synchronous and symmetrical, 2-to-3-per-second activity most pronounced in the frontal regions.* A few days previously an electroencephalographic tracing had been normal.

Similar neurologic disturbances were also noted in patients A. B. and M. H. In the former the tremor predominated. It first appeared on the third day of resin therapy, was present at rest by the ninth day and was marked on the twelfth and last day, at which time the patient also experienced drowsiness and generalized weakness and was mildly disoriented and emotionally labile. A normal mental status was resumed within one day after the resin was discontinued, and the tremor was barely perceptible after four days. Patient M. H. had severe mental disturbance, with disorientation and delirium apparent on the ninth day of resin therapy. At this time she was unaware of her immediate environment and of her position in space. She was drowsy and depressed. In addition, a flapping tremor of the outstretched hands was elicited. All delirium and tremor had subsided one day after resin was stopped, and after several days of drowsiness she was again her usual jovial self.

Patient H. H. was given 600 gm. of resin over a ten-day period. On the tenth day drowsiness, apathy and slurring of speech were noted, but tremor and mental disturbance were not apparent. This patient complained of epigastric burning after each dose of resin and also developed a fecal impaction.

Discussion

Cation-exchange resins induced significant diureses in 10 of 12 patients with cirrhosis of the liver and ascites. However, a prominent complication occurred that was characterized by neurologic disturbances consisting of abnormalities in mental status and the development of a characteristic tremor. This complication occurred only in the patients receiving the resins containing ammonium; it was distinctly different from the syndrome observed in the patients receiving the hydrogen resin, who became frankly hypokalemic and acidotic and displayed clinical evidence of these disturbances. In addition to this evidence that the cation-exchange resins studied are poorly tolerated by patients with severe liver disease, the changes in mental status and, particularly, the flapping tremor observed after administration of ammonium-containing resins are also noteworthy, as these resemble the neurologic changes seen in patients spontaneously developing hepatic stupor or coma.[27] In addition, the alterations in the electroencephalogram observed in the one patient (R. P.) on whom a tracing was made simulated those described in cases of hepatic stupor and coma.[28] Thus it may be difficult, if at all possible, to clinically distinguish resin toxicity from impending hepatic coma. Indeed, the similarity of these two clinical conditions suggests some common biochemical abnormality. The mechanisms involved in the toxic reactions produced by the ammonium-containing resins remain to be determined. Two possible mechanisms may be considered: first, that the toxic effects result from a deficiency of some substance or substances removed by the resin; and secondly, that these effects are caused by an excess of a substance released by the resin. Sodium depletion resulting from resin administration must be considered a possible cause of the neurologic changes observed in these patients. However, the serum sodium concentration was decreased from control levels in only 2 patients (J. L. and A. R.); in these cases neither mental disturbance nor tremor occurred. Although hyponatremia was noted in some patients during the control period, in no case was this accentuated by the resins.

Moderate hypokalemia occurred on two occasions in one of the patients (H. M.) given the ammonium exchange resin (data on the other 3 patients given this resin is not adequate for interpretation). Of the 4 patients receiving the hydrogen exchange resin, marked symptomatic hypokalemia and acidosis occurred in two (J. G. and J. C.), both of whom were on sodium-restricted diets — moderate decreases in serum potassium concentration in one (N. B.) and no alteration in serum potassium in the other (M. S.). In contrast to these patients, however, those given the potassium-containing resin did not develop significant reductions in serum-potassium concentration.

Ammonium is one of the substances released by the resins containing this ion; it is presumably available for absorption. The quantity released may be appreciable, as 60 gm. of resin contains the equivalent of about 9 gm. of ammonium chloride.

*The authors wish to thank Joseph M. Foley of the Neurological Unit, Boston City Hospital, for interpreting the electroencephalogram and for clinically evaluating some of the patients studied.

Since the metabolism of an ammonium salt involves the production of urea by the liver, it is possible that patients with liver disease are not able adequately to remove the ammonium from the blood and that the untoward effects noted in these patients were due to ammonium intoxication. The finding of elevated blood-ammonia levels in some patients with hepatic coma supports this hypothesis,[29] but conclusive evidence is lacking.

Acidosis has been consistently described as following the administration of cation-exchange resins[1-5]; it also developed in some patients in the present study. Although this metabolic consequence of resin therapy may account for some of the findings in the patients studied, such as drowsiness and apathy, it seems unlikely that the tremor and alterations in mental status were related to the acidosis. R. P., for example, on two separate occasions developed a severe flapping tremor after short courses of resin therapy before significant alteration in the serum carbon-dioxide content occurred. M. H. is another case in point. This patient had a serum carbon-dioxide content of 16 mM per liter three days prior to the onset of her delirium, 14 mM per liter at the height of the mental disturbance and 19 mM per liter one day after resin was discontinued and the mental status had returned to normal. Likewise, A. B. had a serum carbon-dioxide content of 23 mM per liter when the tremor was at its maximum and of 22 mM per liter three days later, when the tremor was subsiding. H. H., on the other hand, developed severe acidosis and became drowsy and apathetic but was not confused, disoriented or tremulous.

The data presented are insufficient to warrant definite conclusions concerning the cause of the tremor and mental disturbances observed in those patients receiving the ammonium-containing resins. The similarities between the neurologic findings observed in these patients with liver disease receiving such resins and those noted in impending hepatic coma justify a more careful evaluation of the biochemical alterations induced by these resins.

Summary and Conclusions

Twelve patients with severe cirrhosis of the liver, ascites and edema were observed clinically before, during and after the administration of cation-exchange resins (4 patients, ammonium resin; 4 patients, hydrogen resin; 4 patients, ammonium-potassium resin) given as treatment for ascites and edema. During 18 courses of therapy of 30 to 90 gm. daily in divided doses for from three to thirteen days, 10 of the patients had significant diuresis with reduction in ascites and edema and losses of body weight.

Neurologic disturbances developed on 8 occasions in 6 of the 8 patients receiving the resins containing ammonium. The disturbances, which were noted as soon as three days after the institution of therapy, consisted of drowsiness, apathy, weakness, slurring of speech, disorientation, confusion, inappropriate behavior and a coarse, irregular, flapping tremor intensified by the sustenance of posture. In 2 patients these changes occurred during the first course of resin, cleared promptly when resin was discontinued and recurred on reinstitution of the resin. The tremor usually appeared first and persisted longer than did the alterations in mental status, and the changes were quickly reversed after resin was stopped. The neurologic complications noted did not correlate with alterations in the serum sodium or potassium concentrations or with the degree of acidosis; hence they could not be definitely attributed to these alterations. In contrast, 2 patients given the hydrogen resin had typical clinical manifestations of hypokalemia and acidosis without the neurologic abnormalities observed in the patients given the ammonium-containing resins.

Constipation and fecal impaction occurred frequently as a complication of resin therapy. These must be considered seriously in patients who are predisposed to massive bleeding from esophageal varices or hemorrhoids. Other complaints included one instance of epigastric burning, one of anorexia and two of leg cramps.

The present study indicates that the cation-exchange resins investigated are poorly tolerated by patients with severe liver disease and should be administered cautiously if at all. These resins do not replace an adequate diet rigidly restricted in sodium content as the best method of management of ascites and edema in patients with liver disease.

The similarity of the tremor and mental changes observed in the patients given ammonium-containing resins to the neurologic manifestations of impending hepatic coma suggests a common biochemical basis.

William L. Morgan, Jr., fourth-year student at Harvard Medical School, assisted in several of these studies. The technical assistance of the Misses Meredith Arzt, Alice Ballou, Ellen Doyle and Virginia Olsson is gratefully acknowledged.

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AUDIBLE AURICULAR HEART SOUNDS IN AURICULAR FLUTTER*

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THE bedside diagnosis of auricular flutter can occasionally be made on the basis of certain characteristics of the ventricular rate and its response to carotid-sinus pressure, deep inspiration and exercise, changing intensity of the first heart sound (especially when the ventricular response is irregular) and rapid auricular undulations in the neck veins. Less frequently but more conclusively the diagnosis can be established by the presence of audible auricular heart sounds at the precordium.

Instances of auricular flutter in which auricular sounds have been heard and recorded by graphic methods are rare. In their excellent review of this subject, Hecht and Myers[1] in 1945 discussed 8 cases previously reported and added 2 of their own. The rarity of this auscultatory phenomenon is understandable in view of the fact that untreated auricular flutter is commonly associated with a 2:1 ventricular response, which results in a ventricular rate too rapid to permit the perception of auricular sounds. Higher grades of auriculoventricular block may prolong the diastolic silence of the ventricles enough to favor the detection of auricular sounds. Thus 7 of the reported cases presented the unusual combination of auricular flutter and complete heart block. In the remaining three cases, the sounds of the fluttering auricles were detected when ventricular response varied from 2:1 to 4:1.

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The 2 cases presented by Hecht and Myers are unique in that the auricular sounds were registered from the precordium during ventricular systole as well as during diastole. In each case auricular flutter was accompanied by varying degrees of auriculoventricular block. Levine and Harvey[2] noted the same phenomenon in an instance of auricular flutter with 4:1 ventricular response. In the cases reported below, the auricular sounds are recorded from the precordium in both ventricular systole and diastole in complete heart block, a finding not previously reported, although the registration of this phenomenon by means of an esophageal phonocardiogram in a similar case was reported by Taquini.[3]

CASE REPORTS

CASE 1. A 74-year-old man entered the hospital because of shortness of breath and mild orthopnea of 3 weeks' duration. There was no history of previous heart disease or of rheumatic infection, diphtheria or syphilis. He had never taken digitalis. Physical examination revealed an elderly, somewhat obese man in no acute distress. There was slight tortuosity of the retinal arterioles and moderate thickening of the brachial arteries. The cervical veins were somewhat distended and exhibited a strong positive venous pulse rate of 30. In addition, small, rapid flutter waves were detectable. Physical and roentgenologic examination revealed generalized cardiac enlargement and some pulmonary congestive changes. The rate at the apex was 30 and the rhythm was regular. A Grade II apical systolic murmur was transmitted to the left axilla, and a Grade II aortic systolic murmur was transmitted to the neck. Changing intensity of the first heart sound was noted. In the second intercostal space, close to the left sternal margin, rapid and regular clicking sounds were heard. The sounds were noted to be faint in early diastole, becoming louder before the first heart sound. The blood pressure was 210/80.

The electrocardiogram revealed auricular flutter with an auricular rate of 270 and complete heart block with a ventricular rate of 30. An electrocardiogram and a phonocardiogram were taken simultaneously, with the chest piece recording sounds at the second left intercostal space near the sternal border (Fig. 1).

Case 2. A 49-year-old woman was admitted with generalized congestive heart failure, marked cardiomegaly and complete heart block. There was no history of rheumatic or diphtheritic infection, but the complete heart block had been known to be present since childhood. Serial electrocardiograms revealed complete heart block with a ventricular rate of 46. The rhythm of the auricle was dominantly that of auricular fibrillation but after mild exertion typical flutter waves were observed in the neck veins, and rapid auricular sounds of tic-tac quality could be heard at the base of the heart at the second intercostal space on either side of the sternum. No change in intensity of the auricular sounds was detectable by auscultation. No murmurs were heard. Electrocardiograms at this time confirmed the presence of auricular flutter with an auricular rate of 370. A simultaneous phonoelectrocardiogram was taken, with the chest piece recording sounds at the second left intercostal space near the sternal border (Fig. 2).

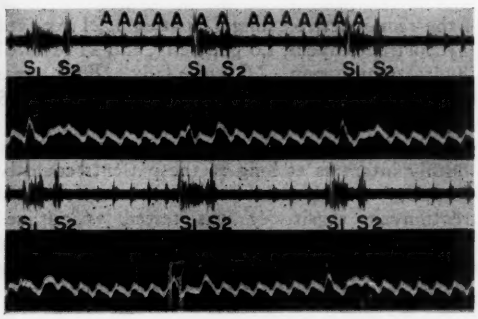

Figure 1. *Simultaneous Phonoelectrocardiogram in Case 1.*

Discussion

In addition to featuring the recording of auricular sounds in ventricular systole as well as in diastole in auricular flutter with complete heart block, these cases are of further interest in that the phonocardiogram in Case 1 confirmed the clinical observation of a graded increase in intensity of the auricular sounds during ventricular diastole. In both cases the amplitude of the auricular sounds registered in the early diastolic phase was relatively low and gradually increased as ventricular systole was approached, attaining the greatest intensity in those auricular sounds that occur during ventricular systole. This graded increase in amplitude was fairly constant in each recorded cardiac cycle and was determined to be unrelated to the respiratory cycle.

It appears likely that this phenomenon is in some way related to changes in the position of the auriculoventricular valves during the ventricular filling phase. At the moment of opening of the auriculoventricular valves early in ventricular diastole, the gradient between auricular and ventricular pressures is maximal and the auriculoventricular leaflets are at their lowest position in the ventricular cavity. As filling of the ventricles progresses, a gradual decrease in the auriculoventricular gradient is accompanied by a gradual ascent of the leaflets toward the closed position. This explanation of the graded intensity of the auricular sounds is supported by the observation that the loudest auricular sounds are heard during ventricular systole when the auriculoventricular valves are in the closed position.

Summary

Two cases of auricular flutter in which audible auricular sounds were graphically recorded are added to the 11 cases previously reported.

These cases are of interest in that auricular sounds were recorded at the precordium during ventricular systole in complete heart block, a finding not previously reported, and a graded increase in intensity of the auricular sounds in each cardiac cycle was observed and confirmed by phonocardiogram.

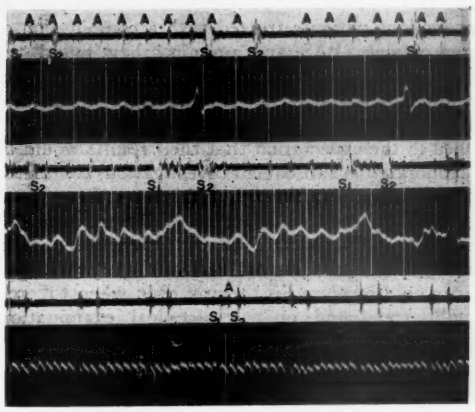

Figure 2. *Tracings Made in Case 2.*

Upper tracing is simultaneous phonoelectrocardiogram at paper speed of 75 mm. per second. Middle tracing is simultaneous recording of jugular pulsations and heart sounds. (Note auricular waves appearing between positive ventricular pulsations.) Lowest tracing was made at standard paper speed of 25 mm. per second. (Note that auricular sounds during ventricular systole are of maximal amplitude.)

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EFFECT OF COMBINED THERAPY (DIHYDROSTREPTOMYCIN AND PAS) ON THE EMERGENCE OF STREPTOMYCIN-RESISTANT STRAINS OF TUBERCLE BACILLI*

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AMONG students of tuberculosis the opinion is generally held that the addition of PAS to streptomycin regimens will delay or actually prevent the emergence of resistant strains of tubercle bacilli. The value of combined therapy (streptomycin and sulfonamides) had been amply demonstrated in the case of nontuberculous infections such as brucellosis[1] as early as 1948, although the exact modus operandi had not then been defined. It seemed possible to us at that time that a similar line of reasoning might be applied to the therapy of pulmonary tuberculosis, but it was not until February, 1949, that Karlson and his co-workers[2] at the Mayo Clinic demonstrated that this was indeed the case. In a study of 14 tuberculous patients treated with a combination of streptomycin, PAS and promin, they found the emergence of resistant strains of tubercle bacilli to be appreciably delayed. This paper took the form of a preliminary communication, which was published in the expectation that their results would be corroborated in subsequent investigations conducted on a larger scale. Since then, however, few reports on the subject have appeared. This may well be due to the difficulty, frequently experienced, of obtaining positive cultures from the sputum of patients on streptomycin therapy even when tubercle bacilli are found on microscopical examination. Early in 1949 we embarked on a study that we hoped would supply satisfactory evidence for or against that thesis; this paper embodies the results of almost two years of investigation of the problem.

Material and Methods

Fifty patients with pulmonary tuberculosis constituted the material for this study; 26 were males and 24 females. Their ages ranged from fourteen to sixty-seven years. Six were classified as moderately advanced, the remainder being far advanced. The fact that the majority of patients had far advanced disease was due to our method of selection, subjects being chosen who for various reasons were considered unfit for any form of collapse therapy and who might be expected to produce a positive sputum at the conclusion of the study. All patients were treated for three months. A "control" group consisted of 18 patients; 8 received a daily dose of dihydrostreptomycin, 1.0 gm., and 10 received a daily dose of dihydrostreptomycin, 2.0 gm. The only exception was 1 patient (Case 7), who had received streptomycin in another institution before being transferred to this hospital. None of the patients in this group received PAS. Of the remainder, totaling 32 patients, 21 received dihydrostreptomycin, 1.0 gm. daily, and 11 received dihydrostreptomycin, 2.0 gm. daily. Both these latter groups received, in addition, 5.0 gm. of PAS daily.

Sputum specimens were collected for culture at monthly intervals as long as the patients could be followed; when positive cultures were obtained streptomycin sensitivity was tested as outlined below. After preliminary concentration by the trisodium phosphate method, primary culture was carried out on either Petragnani or Lowenstein-Jensen medium. After satisfactory growth had occurred, colonies were subcultured in Dubos liquid medium. After four days subcultures from the resulting diffuse growth were made in tubes of Herrold's egg medium, containing graduated concentrations of dihydrostreptomycin — 0, 1, 10, 50 and 100 microgm. per cc. of medium. The details of this technic of determining streptomycin sensitivity have been described elsewhere.[3] Organisms were considered resistant when growth occurred in the presence of a concentration of dihydrostreptomycin greater than 10 microgm. per cc. of medium.

Results

The results of this study are summarized in Table 1. It will be noted that in the combined therapy group the persistence of sensitivity or the emergence of resistance appeared to bear no relation to the character of the disease (caseous-cavernous or otherwise). This feature will be discussed in subsequent paragraphs. A large proportion of patients who remained sensitive were followed for periods varying from nine to sixteen months after institution of treatment. Of the original 50 patients, there were 17 in whom we were unable to obtain tubercle bacilli on culture after completion of treatment. Of these 17, 7 were members of the control group; the remainder had received combined therapy. There was, in addition, 1 patient whose cultures were resistant from the outset. The results with regard to streptomycin sensitivity, therefore, apply to 32 patients only. Of these 32 patients, 11 fell into the control group and 21 received combined therapy. Of the 11 patients in the control group, 2 were found to be sensitive and 9 resistant. Of the 21 patients in the combined therapy group, 15 were sensitive and 6 resistant.

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TABLE 1. *Effect of Combined Therapy (Dihydrostreptomycin and PAS) on the Emergence of Streptomycin-Resistant Strains of Tubercle Bacilli.*

Case No.	Sex	Age	Caseous-Cavernous Disease	Diagnosis	Dihydrostreptomycin, 1.0 gm. — No. of months after beginning of treatment															Result
					0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
		yr.																				
1	F	24	+	Far advanced	S*		R*		R	R		S										S
2	M	42	+	Far advanced												R						R
3	M	37	+	Far advanced								R	R									R
4	M	30	+	Far advanced										R								R
5	M	19	+	Far advanced	S	S	S		S	R	S	S						R				R
6	M	60	+	Far advanced	R	R	R	R			S	R										R
7	M	58	+	Far advanced																	R	R
Sensitive ..... 1 Resistant ..... 5 Resistant throughout 1																						
				Dihydrostreptomycin, 2.0 gm.																		
8	F	26	+	Far advanced	S			R														R
9	M	56	+	Far advanced	S						R	S										S
10	M	47	+	Far advanced	S		S	R				R										R
11	F	14	+	Far advanced	S				R	R		R										R
12	F	25	+	Far advanced	S		R															R
Sensitive ..... 1 Resistant 4																						
				Dihydrostreptomycin, 1.0 gm., and PAS, 5.0 gm.																		
13	M	37	+	Far advanced			S	S			S	S	S	S								S
14	F	21	−	Moderately advanced	S							S										S
15	M	54	−	Far advanced		S	R		S	R						R						R
16	M	34	+	Far advanced	S	S	S	S	S													S
17	F	23	+	Moderately advanced	S								S									S
18	M	65	+	Far advanced	S			S														S
19	F	27	+	Far advanced	S										S							S
20	M	64	+	Far advanced	S	S			S				S	S		S						S
21	M	43	+	Far advanced						R	R											R
22	M	48	+	Far advanced		S											S					S
23	M	20	+	Far advanced			S		S			S	S	S								S
24	M	45	+	Far advanced	S	S				S												S
25	M	39	+	Far advanced	S					S			S	S		R						R
26	F	45	+	Far advanced		S	S					S										S
Sensitive ..... 11 Resistant ..... 3 Caseous-cavernous Sensitive ..... 10 Resistant 2																						
				Dihydrostreptomycin, 2.0 gm., and PAS, 5.0 gm.																		
27	M	39	+	Far advanced	S			S						S	S							S
28	F	24	+	Far advanced	S	S				R	S	R										R
29	F	19	−	Far advanced	S							S	S									S
30	M	49	+	Far advanced	S							R										R
31	M	60	+	Far advanced	S	S	S	S	R		S										S	S
32	M	50	+	Far advanced	S		R	S	R													R
33	M	27	+	Moderately advanced	S						S										S	S
Sensitive ..... 4 Resistant ..... 3 Caseous-cavernous Sensitive ..... 3 Resistant 3																						

TOTALS

Control group (11 cases): sensitive, 2; resistant, 9.
Combined-therapy group (21 cases): sensitive, 15; resistant, 6.

*S = sensitive; R = resistant.

Discussion

It seems clear that the addition of PAS in 5.0-gm. daily doses to the prolonged streptomycin regimen used in this study resulted in a great diminution or delay in the emergence of resistant strains of tubercle bacilli. It is generally conceded that in any group of patients receiving streptomycin in daily doses of 1.0 or 2.0 gm. for three months 80 per cent will become resistant by the end of that period[4]; this is mirrored by the results in our own control series. By this criterion, if PAS had not been employed the expected figures in our test group would have shown 17 to be resistant and 4 sensitive rather than 6 resistant and 15 sensitive, which was actually the case with combined therapy. Our results are rather similar to those of Anderson, Jansen and Wicks,[5] with the rather significant difference that they used a 10.0-gm. daily dose of PAS, in contrast to our 5.0 gm., and found it necessary to discontinue PAS in several cases because of toxic reactions. In our series no patient was unable to tolerate a 5.0-gm. daily dose of PAS, and, as a measure for reducing the development of resistance, the 5.0-gm. daily dose appears to produce satisfactory results. It seems wise, therefore, to initiate combined therapy with a 10.0-gm. daily dose of PAS, reducing it to 5.0 gm. if the larger dose is not tolerated.

Adcock and others[6] found that the use of streptomycin-paramino-salicylate did not result in the prevention of streptomycin resistance. However, the total daily dosage of PAS embodied in this chemical combination amounts to only 0.8 gm. These workers' results are therefore not comparable with those of any regimen embodying the use of moderate or large doses of PAS.

In the course of this study it was noted that primary cultures were in many cases impossible to obtain during combined therapy, although tubercle bacilli could at the same time be demonstrated microscopically in the sputum. This phenomenon has been noted by other observers[7]; it made it necessary for us to follow our cases for a much longer period than has usually been done. However, this circumstance has provided us with the additional information that streptomycin resistance may be delayed for a year or more after completion of combined therapy, thus greatly extending the safe period for possible major surgery.

An interesting finding, which we were at first unable to explain, was the occasional occurrence of resistant cultures in patients whose earlier and later cultures were unmistakably sensitive. Although we were at first inclined to attribute this to laboratory error, we later found that other observers had had similar experiences.[8] It seems possible that this result is based on the sampling of organisms from different loci in a tuberculous lung, those from one locus being sensitive and those from another being resistant.

In recent studies, various workers[9-11] have indicated that bacterial resistance is more likely to emerge in lesions with frank caseation or cavitation than in noncaseous disease. We would, however, point out that the great majority of our patients on combined therapy had caseous-cavitary lesions and that we noted no higher incidence of resistance in these than was found in the noncaseous lesions. It seems, therefore, that the addition of PAS to streptomycin regimens is of distinct value in delaying the development of bacterial resistance, even under the least favorable circumstances.

Summary

Fifty patients with moderately advanced and far advanced pulmonary tuberculosis were treated with dihydrostreptomycin alone and in combination with PAS. Seventeen of these constituted a control group; they received dihydrostreptomycin alone. The remainder received dihydrostreptomycin, 1.0 or 2.0 gm. daily, and PAS, 5.0 gm. daily. The duration of therapy was ninety days in all cases.

Streptomycin-sensitivity tests were carried out at monthly intervals in both the control group and the combined-therapy group, and several patients were followed for as long as sixteen months.

Of 21 patients in the combined-therapy group in whom positive cultures were obtainable after treatment had been completed, 15 remained sensitive and 6 were resistant. In the control group, of 11 suitable patients 2 were sensitive and 9 resistant.

These results indicate that the addition of PAS to streptomycin regimens is of great value in preventing or delaying the emergence of bacterial resistance.

Addendum

Since this paper was written, two articles have been published on this subject: that of Beck[12] and that of Louis and his co-workers.[13]

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MEDICAL PROGRESS

HORMONAL TREATMENT OF CANCER*

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AN INTIMATE relation between steroid hormones and the genesis and course of certain tumors may be regarded as established. Recent developments have stimulated extensive exploration of the potentialities of steroids in the etiology and treatment of cancer.[1-12] It is generally acknowledged that induced alterations in the hormonal balance of patients with advanced stages of some neoplasms may significantly modify the anticipated behavior of the tumor. It should be emphasized that this modification can be in the direction of either temporary regression or distinct acceleration of the disease. This report is a summary of the extensive literature that has accumulated on the subject in the past seven years.

It is perhaps significant that thus far only 5 types of neoplastic disease appear to be altered in their usual course by hormonal therapy; these are malignant lesions of the breast, prostate gland, uterus and lymphatic and hematopoietic systems. Many patients with these forms of neoplastic diseases, nearly all unsuitable for surgical and radiation therapy, have been subjected to hormonal treatment. Careful histologic, cytochemical and metabolic studies have been made on a number of these patients in an attempt to elucidate the mechanisms of hormonal alteration on the tumor as well as on the host. An exact, irrefutable explanation is not as yet available, although several feasible theories have been developed and will be presented under individual headings.

Although the mechanisms of action of hormonal administration or deprivation on cancer have not been defined, certain criteria for the selection of patients and for dosage schedules are now available. In spite of adherence to these criteria, the response of a given patient to this form of therapy is unpredictable.

The following general principles of indications for hormonal therapy have been listed previously[13] but bear repetition: A thorough knowledge of the natural behavior of neoplasms is essential for an understanding of the role and rational use of hormones as a method of treatment. No cancer deemed curable by established methods should be considered for trial with experimental procedures, such as hormone therapy. Hormones can be administered as a primary treatment when the initial localized manifestations have advanced beyond effective palliative control through orthodox methods of surgery and irradiation. Treatment with hormones may also be considered an adjunct to the methods of proved value, especially when the disease has become distant or disseminated in its manifestations. Since endocrine therapy has definite limitations and may sometimes cause serious complications, additional and intensive studies must be made before it is generally accepted.

CARCINOMA OF THE BREAST

Castration

Castration, performed either surgically or by radiation, has become an accepted addendum to the treatment of carcinoma of the breast in advanced stages of the disease.

Prophylactic castration. There is general agreement that prophylactic castration does not increase the curability rate of those patients in whom radical mastectomy is performed for a cancer apparently confined solely to the breast or regional lymph nodes. Certain authors, however, take exception to this point of view and strongly advocate castration as a preventive measure.[14-17] Postulating that recurrences are due to cells remaining after radical mastectomy, which are stimulated by estrogens, and that estrogenic stimuli should be removed while few such cells remain, Horsley favors ovariectomy at the time of primary radical surgery.[16, 17] The relatively less satisfactory results of therapy in premenopausal patients and the apparent promotion by pregnancy and lactation of recurrences or carcinoma in the remaining breast of patients already subjected to radical mastectomy for cancer are cited as additional reasons for recommending prophylactic castration. In a series of 39 premenopausal women treated by simultaneous radical mastectomy and bilateral ovariectomy, the five-year "cure" rate was reported as 76.9 per cent. Sicard[14] studied 55 women prophylactically castrated, either surgically or by x-ray. Of these, 41 have shown no evidence of recurrence in six months to three years after radical mastectomy. These latter data should be surveyed critically, especially on the basis of existing statistics.

Therapeutic castration. There is no doubt that effective ovarian irradiation or ovariectomy may be of material benefit, resulting in relief of symptoms, objective responses and possible increased life expectancy in premenopausal patients with advanced

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primary, recurrent or distant metastatic breast cancer. In our experience, some women castrated a few years after spontaneous cessation of the menses have also had gratifying responses. These patients showed evidence of residual ovarian activity. Most of the data indicate that from 15 to 30 per cent of patients obtain palliative benefit from castration.[14-16, 18-24] Halberstaedter and Hochman,[20] however, report improvement in 56 per cent of a series of 60 cases. The observations include both symptomatic and objective responses. Sicard's figures[14] in a smaller series are similar. The larger series of Adair and others,[19] comprising 335 women castrated either because of metastatic cancer or for unrelated pelvic conditions revealed a 15 per cent survival rate of two or more years after the appearance of osseous or soft-tissue metastases. The favorable responses to castration are variable in duration, lasting from a few months to several years. The discrepancies in the percentages of favorable effects reported by various observers may be partially explained by the composition of the series (especially as regards prophylactic or therapeutic castration), differences in classification of response and variation in extent and manifestations of the disease.

Method of castration. In evaluating the efficacy of castration, the method by which it is achieved must be taken into consideration.[24] Both ovariectomy and irradiation of the ovaries have been employed. It is obvious that methods short of ovariectomy do not permit critical analysis of the effect of complete eradication of gonadal function. Varying degrees of ovarian suppression may be attained by radiation therapy; this is apparently dependent on the dosage as well as on other factors.[25] Therefore, knowledge of the state of gonadal function is of prime importance in evaluating responses of the tumor after ovarian irradiation. The development of amenorrhea and other menopausal symptoms after irradiation of the ovaries are not adequate criteria of the completeness of ovarian suppression. Studies of urinary gonadotropins, estrogen excretion and vaginal smears after such treatment not infrequently reveal considerable fluctuation, as contrasted to relatively constant low levels after ovariectomy.[25] Furthermore, even though these criteria may suggest initially that complete ovarian suppression has been achieved, the menses may reappear and menopausal symptoms vanish, indicating functional recovery.

The failure to suppress ovarian function completely and permanently by means of radiation is due in part to insufficient dosage. Young women, because of greater ovarian activity, require a higher dose level than women in the late phases of their menstrual life. There is good evidence that radiation dosage individualized for a particular case may be as efficacious as surgical castration. Because of the uncertainty, however, there has been a trend toward ovariectomy in young women when their condition permits it, reserving radiation for women over forty, when ovarian activity is beginning to wane.

The effectiveness of ovarian irradiation can be followed by serial studies of the vaginal smear. In most cases a minimum of six to eight weeks is usually necessary to achieve effective ovarian suppression by radiation technics. Ovariectomy, therefore, is preferable if a rapid clinical effect is desirable because of acute and disabling symptoms. When this was not feasible, we have used testosterone in conjunction with radiation to hasten suppression of ovarian function.[24] This may be accomplished by inhibiting pituitary gonadotropic activity or by suppressing action of ovarian hormones either in the circulation or in the tissues or by a combination of these effects. Thus, in this instance, testosterone is used primarily for this purpose and hence is discontinued in about two months, when the optimum effects of radiation have presumably been obtained. As will be mentioned later, other actions of androgens are of distinct value also; hence they may be of additional aid during this period.

Testosterone therapy may be used solely to suppress ovarian function, but there is no proof that it is as efficacious as castration by surgery or radiation. Actually, we have seen more definite or further benefit when either ovariectomy or ovarian irradiation has been employed after initial androgen therapy. Likewise, androgen therapy has produced a further respite in patients in whom radiation therapy to the ovaries was first used but in whom it was apparently ineffective in completely suppressing ovarian function.

The use of testosterone concomitantly with prophylactic castration has also been advocated.[26, 27] Sicard[26] recommends the implantation of testosterone pellets at the time of castration. Snapper[27] concluded, from a series of 13 patients followed one year or more after combined radical mastectomy, castration and testosterone, that this therapy does not protect against the development of metastases in patients with positive axillary nodes at the time of surgery.

Effects of castration. Patients responding favorably to castration may show improvement in general physical condition, increase in appetite and weight, relief of pain and rehabilitation. Primary, lymph-node and other soft-tissue lesions may undergo marked regression, and osseous lesions may calcify. Stimulation of hematopoiesis may lead to the return of hemoglobin to normal levels in patients with anemia secondary to osseous involvement. Some patients obtain excellent subjective relief without any demonstrable objective changes; others have marked regression of the detectable lesions.

Mechanism of effects of castration. It is generally agreed that the most plausible reason for the effectiveness of castration in advanced breast cancer

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is the withdrawal of some specific stimulating effect that estrogens or unknown ovarian hormones have on the abnormal, as well as the normal, cells of the mammary gland. There is also the possibility that eradication of the ovarian steroids will permit hormones of other endocrine organs, particularly the adrenal glands, to exert an effect on the tumor. Halberstaedter and Hochman[20] speculate that the withdrawal of estrogens probably diminishes the vitality of the malignant cell, giving the natural defenses of the body an opportunity to overcome the tumor cells. It is possible that complete ablation of ovarian function is not necessary, since favorable effects on breast cancer are not infrequently seen after apparently inadequate radiation to the ovaries. This may be due to a suppression of the sensitive estrogen-producing follicular apparatus without an effect on the relatively radioresistant stromal elements that appear experimentally to be a source of androgenic hormones.[24] The ovary may thus play a dual role. That all favorable results are inevitably vitiated by a resurgence of the disease may be attributable to the endogenous production of estrogens from other sources.

Castration for cancer of the male breast. Cancer of the breast in the male is frequently in the advanced stage when first seen. Orchiectomy in these cases and in recurrent cases has generally resulted in effects more striking than those following ovariectomy in female breast cancer and are akin to those seen after castration in carcinoma of the prostate gland.[28-33] As in the female, osseous lesions respond particularly well, but favorable influences have also usually been observed on the primary lesion, lymph nodes and pulmonary metastases. A few cases have been followed for five years without sign of reactivation.[29] In contrast to females, castration in males appears to be more efficacious in the older age group.

Orchiectomy is undoubtedly more effective than radiation in obliterating testicular activity. Even intensive irradiation seldom completely suppresses the androgenic function of the male gonads. This is apparently due to radioresistance of the interstitial cells, the presumed source of androgens in the testes. Moreover, severe radiation reactions that may occur in the sensitive scrotum are to be contrasted with the comparatively simple procedure of orchiectomy, which offers relatively little risk even in patients who are in poor general condition.

Androgens

Experiments in animals and human beings indicated that androgens should be subjected to extensive clinical trial in breast cancer.[1] This was fortified by clinical reports from Loeser[34] and Ulrich[35] and, later, from Fels[36] on the effect of androgens on breast cancer, which suggested trial of these agents in the therapy of widespread carcinoma of the female breast. Farrow and Woodard,[37] using moderate doses of testosterone propionate for brief periods, noted occasional symptomatic benefit without objective effect on the primary tumor or its metastases. Adair and Herrmann,[38] using larger doses over longer periods, reported definite objective responses in a few patients in a small group with advanced breast cancer. As a result of these early studies, sizable series of cases treated with these agents have accumulated in the past six years.[14, 21, 26, 36, 38-75] The most significant statistical evaluation of androgen therapy is being conducted by the Subcommittee on Steroids and Cancer of the Committee on Research of the American Medical Association.[55-57]

Prophylactic use of androgens. Just as prophylactic castration has been advocated by several workers, androgens have also been administered in an attempt to defer or prevent the development of recurrences after primary surgery. Sicard[26] and Snapper,[27] as mentioned above, have tried combining castration and testosterone administration, without apparent additive benefit. Prudente[76, 77] has presented statistics to support his advocacy of the prophylactic use of androgens after radical mastectomy. The plan of therapy is based on the histologic grade of the cancer, the clinical stage, the age and the menstrual cycle. In the second publication the data are not as convincing, particularly as regards adequacy of follow-up information. This work needs confirmation. Anglem and Lawrence[78] have initiated prophylactic testosterone therapy in a smaller series of cases, but it is too soon to draw conclusions from this material.

Therapeutic use of androgens. Androgens have been used primarily as palliative agents in advanced mammary cancer with metastases. In the selection of appropriate patients for androgen therapy, age is not an important determining factor, as these agents may exert a favorable effect in any stage of life. The site of disease is of prime importance, as androgens exert their major favorable effects on osseous metastases and the symptoms arising therefrom.

Drugs and dosage. Present clinical experience has been obtained largely through the use of testosterone propionate by intramuscular injection. The usual dosages recommended have been 150 to 300 mg. weekly in three divided doses, although some investigators[67, 79] have advocated much larger doses (100 to 200 mg. daily) in cases apparently refractory to the lower range. The Subcommittee on Steroids and Cancer selected four schedules for investigation consisting of 25, 50, 100 and 200 mg. three times weekly and found no significant difference between the lowest and highest schedules.[57] The data, based on therapy of 441 patients, suggest that 150 mg. per week is adequate. The analysis suggests also that response is more closely correlated with duration of treatment than with total dosage and that three months is the minimum treatment period within which a favorable response may be observed. This has been the personal experience of the au-

thors.[24] Because the duration of both androgenic and estrogenic therapy is debatable, a discussion of this aspect will be deferred until estrogenic therapy has been discussed.

Testosterone propionate has been used most commonly as a means of androgenic therapy, but other preparations have received trial, parenterally and orally. Crystalline suspensions of testosterone,[64] methyl testosterone[47, 57] and testosterone cyclopentyl propionate[80] appear to be as effective as testosterone propionate when given in comparable dosages. Each of the compounds is an active androgen. Some of the effects of the more active androgens are undesirable in treating patients with breast cancer (this will be discussed later). Thus, compounds are being sought and tested that may produce favorable tumor and metabolic responses without eliciting other and ineffective changes that are distressing to the patient. Among these latter compounds methylandrostenediol and dihydrotestosterone, allied to testosterone, have been reported as eliciting favorable objective and subjective responses.[81, 82] Data from three series of cases[83-85] indicate that methylandrostenediol in the dosages utilized is not nearly as effective as testosterone, even though it may elicit metabolic and (to a certain extent) other effects characteristic of androgens. The findings indicate that this compound should be classified as a mild androgen. Sufficient data have not been accumulated on dihydrotestosterone to warrant any conclusion. This compound appears to be more effective therapeutically than methylandrostenediol.[86] It is probably more active as an androgen and hence may more nearly simulate the effects of the better known preparations. Compounds with these characteristics deserve further investigation, but in order to be of real value a compound should be at least as good as or better than testosterone without producing its undesirable side-effects. This may be difficult to achieve; our own studies thus far indicate that the best responses of breast cancer are intimately associated with the androgenic activity of a compound, irrespective of purely metabolic capacities.

Effects of androgen therapy. Androgen therapy appears to be most efficacious in patients with osseous metastases, regardless of the patient's age. Symptomatic improvement may appear within two to four weeks, with marked alleviation of pain, increase in appetite and weight, improvement in mental attitude, freedom from dependence on narcotics and rehabilitation occurring in a high percentage of cases. Unfortunately, there is considerable discrepancy between subjective and objective improvement in response to these compounds. Calcification of osteolytic lesions is demonstrable in only 20 to 25 per cent of the cases treated, although it is possible that changes occur that cannot be detected radiologically. Evidence of recalcification is not usually discernible by x-ray examination for three to five months after the institution of treatment. As evidence of bone repair and regeneration, the serum alkaline phosphatase may rise from the normal value of 3 to 5 units per 100 cc. to 15 to 20 units, and calcium balance may change from negative to positive. This usually occurs earlier than the radiologic changes. Coincidentally with these favorable effects there may be a hematopoietic response, with improvement in anemia secondary to bone-marrow involvement. The bone marrow in such cases shows increased erythroid activity, which at times returns to normal and occasionally approaches polycythemia. In some cases, as the original lesions apparently continue to improve, new osteolytic lesions may develop and progress. Other patients, although enjoying excellent symptomatic relief, may show steady progression or even acceleration of osseous disease.

Soft-tissue lesions, primary or recurrent in the breast or involving the skin, lymph nodes, pleura, lungs, liver and brain, may undergo impressive and occasionally prolonged regression. The percentage of patients who enjoy these objective responses is for practical purposes approximately the same as or slightly less than that noted in persons with osseous lesions. In our experience, soft-tissue remissions occur oftener in premenopausal patients, although other workers report no correlation with the menopausal status.

The duration of favorable responses of osseous or soft-tissue disease is variable, but in the majority of cases recrudescence of the signs and symptoms appears within a year. Some patients, however, have enjoyed sustained benefit for several years.[24] The Subcommittee data[57] indicate that the mean survival of patients responding to testosterone propionate is twice that of patients not responding to treatment.

Side-effects of androgen therapy. The administration of such large doses of potent androgenic agents to the female patient does not leave her undisturbed physically, chemically, metabolically, hematologically, emotionally or cosmetically. Regardless of the response of the neoplastic tissue *per se*, a train of events altering the patient as a whole usually ensues in the wake of testosterone therapy. Although commonly classified as "side-effects," they might more properly be regarded as the almost inevitable results of the administration of an agent capable of producing major systemic alterations. The development of some of these alterations is certainly more predictable than are the desired therapeutic effects that prompt their utilization.

The most frequently observed effects of testosterone are attributable to its masculinizing qualities. The rapidity and degree of development of these changes vary considerably among patients. Hirsutism, acne, hoarseness, thinning of the hair and enlargement of the clitoris are common. Increase in libido is often marked in patients of all ages and

may be severe enough to require termination of therapy. Temporary amenorrhea in premenopausal females is usual.

Among the more serious and fortunately less common of the systemic effects of androgens are the precipitation of congestive heart failure and of serious degrees of hypercalcemia. The former is the result of certain properties of androgens, leading to retention of sodium, potassium, chloride and water. If these effects are anticipated, serious sequelae can usually be avoided by using a low-sodium diet and diuretics. Edema of the arm, the drainage of which has been compromised by previous radical mastectomy, may be initiated or aggravated. This complication may also be controlled to some extent by these measures.

Hypercalcemia has been noted by many workers who have treated a considerable number of cases.[59,-67, 87-90] The hypercalcemic syndrome of nausea, vomiting, dehydration, atonicity, apathy, drowsiness and coma, sometimes leading to death, has been well described. This complication occurs only in the presence of osseous involvement. The earliest signs may be subtle; hence the onset of any of the less profound symptoms in patients with osseous lesions should lead to prompt suspicion. Hypercalcemia is most frequently observed early in the course of therapy in patients with extensive osteolytic metastases, particularly if they are confined to bed, but may occur later in the course of continued therapy. Furthermore, it may occur with re-establishment of androgen therapy in patients in whom an initial trial was beneficial and had no such effect. The reasons for these variations are obscure; they are the subject of considerable study and of speculations that have not been resolved and do not warrant discussion here. Hypercalcemia, however, occurs spontaneously in about 10 per cent of cases with osseous metastases from breast cancer.[59, 87, 90, 91] Of considerable interest is the observation that in some cases of spontaneous hypercalcemia the syndrome may be corrected by testosterone administration and is usually accompanied by a favorable effect on the disease. Some workers[58] believe that underlying renal disease is a prerequisite to hypercalcemia, but we have observed both spontaneous and induced hypercalcemia without detectable evidence of renal dysfunction. The serum calcium should be checked prior to and frequently during testosterone treatment; treatment should be withheld or withdrawn if the level rises during therapy. Therapy for this syndrome consists of the intravenous administration of a 2.5 per cent solution of sodium citrate with adequate quantities of dextrose and saline.

Other metabolic effects. In patients with osseous disease, blood chemical changes may occur during androgen therapy that are often significantly informative. The alkaline phosphatase in favorable cases often rises, indicating bone repair and regeneration, but a rise above 20 to 25 units per 100 cc. may signify hepatic involvement. The serum phosphorus, which frequently is high normal or elevated, often falls coincidentally with a favorable response during therapy. In some patients it may return to very high levels, which usually signifies reactivation of disease and is often followed by rapid death. Testosterone may induce positive nitrogen balance in patients initially in a negative phase. This does not necessarily mean that there is an effect on the tumor itself but can be partially explained by the known capacity of androgens to enhance nitrogen storage and to diminish nitrogen output.

Because the favorable or unfavorable responses of carcinoma of the breast to testosterone and estrogens are possibly related and founded on a common (although as yet not clearly defined) basis, comments on the possible mechanisms of action of androgens will be deferred until estrogen therapy has been discussed.

Estrogens

Estrogens, originally regarded as important factors in the development and growth of breast cancer, were first demonstrated in 1942[92] to have an inhibitory effect on established lesions as well. This challenged the earlier concepts and provided impetus to a more thorough investigation. In 1944 one of the authors[1] reviewed the clinical evidence relating the incidence of cancer of the breast to age, early castration and menopause and discussed the first attempts with hormone therapy. At about that time the first data on the modification by estrogens of inoperable carcinoma of the breast appeared. Since then, large series have accumulated.[2, 3, 9, 52,-54-59, 61, 62, 66, 68, 73, 93-101]

Drugs and dosage. A considerable number of natural and synthetic estrogenic preparations have been utilized in the treatment of breast carcinoma. Those being tested under the sponsorship of the American Medical Association Subcommittee include, with their comparative doses: diethylstilbestrol, 15 mg. daily; ethinyl estradiol, 3 mg. daily; Premarin, 30 mg. daily; estradiol dipropionate, 5 mg. twice weekly, intramuscularly; dienestrol, 15 mg. daily; dimethyl ether of diethylstilbestrol, 30 mg. daily; and tri-para-anisyl-chloroethylene (TACE), 24 mg. daily.

Estradiol benzoate, monomethyl ether of diethylstilbestrol, sodium estrone sulfate, hexestrol and benzestrol have also been used. By far the largest experience has been with diethylstilbestrol, but comparable results have been obtained with most of the other compounds. The optimum dose level appears to be in the range of 15 mg. daily of stilbestrol or its equivalent with the other compounds, although smaller doses have been reported to be effective.

Effects of estrogen therapy. The available data serve to emphasize the marked variability in the

response of the disease to estrogens, but, as will be seen, this depends considerably on the physiologic status of the patient. There may be regression, retardation or acceleration of the lesions. Favorable systemic responses, though less frequent than with androgen therapy, are manifested by an increase in appetite and weight, relief of pain and rehabilitation. In contrast to therapy with androgens, there is considerably less discrepancy between objective and subjective response. Well defined objective changes in soft-tissue lesions in carefully selected patients are observed more frequently and are usually more obvious with estrogens than with androgenic therapy. Epithelialization of ulcerated lesions may occur, and gross masses may undergo regressive changes with or without diminution in size, in either case becoming softer and fibrotic to palpation. Lymph-node metastases and pulmonary lesions may diminish in size or apparently disappear. Osseous lesions in selected patients also respond. Osteolytic metastases may undergo calcification and primary osteoblastic processes may apparently become less dense. In both instances there may be a return toward normal bone architecture. Several reports[55-57, 75] indicate some degree of subjective relief in 40 to 60 per cent of patients. About 50 per cent of the patients with soft-tissue lesions had objective improvement; about 20 per cent with osseous lesions were objectively improved. These data are essentially similar to those published by one of us[24] and others.

The earliest favorable effects may be seen within two to four weeks. The available data indicate that if a response is not noted within three months benefit is unlikely. Hertz,[102] using Premarin intravenously, has presented evidence that this route may hasten the appearance of objective improvement. The American Medical Association Subcommittee series[57] suggests that, as with androgens, duration of treatment is more important than the total dose administered.

The initial response of lesions involving the skin frequently follows a definite pattern.[2, 98] A color change to a red or purplish hue accompanied by softening and flattening of the lesion may be noted within two or three weeks. This response may occur in lesions that regress only slightly as well as in those that undergo profound regression. As regression proceeds, the color darkens until it may assume a dark-brown hue. It may take weeks to many months for a given lesion to undergo this conversion to an apparently inactive phase. As in the case of androgens, while lesions regress in one site progression may be occurring elsewhere. In patients with osseous disease, x-ray signs of improvement may not be discernible for six months. From 20 to 40 per cent of patients with pulmonary lesions in individual series have x-ray evidence of regression, sometimes apparently complete.

The duration of palliative response to estrogens is subject to wide variation. Relapse may occur within a few months, and the majority of lesions reactivate within a year. However, remissions may continue for several years. Unlike androgen responses, which may occur in patients of any age, most of the favorable effects with estrogens are observed in women who are at least five years postmenopausal; in the elderly they can be predicted in a relatively high percentage of cases.[24, 55-57] In the premenopausal group, estrogen administration may accelerate the disease or be entirely ineffective. Rarely, a favorable response may be noted. In the intermediate group of women approaching, within or just past the menopause, the effects are variable, ranging from occasional acceleration to definite benefit. It has been shown[10, 98] that the menopausal age of the patient correlates more closely with the percentage of response than the chronologic age. It has been suggested, therefore, that a division be made on the basis of the physiologic status of the patient.[10, 98] Because of this pronounced relation between the effect of estrogen and the menopausal age, investigators have recommended that estrogen therapy be limited to patients at least five years beyond the natural or artificial menopause.[9, 24, 57, 98]

Side-effects of estrogen therapy. The side-effects of estrogen therapy are generally not as dramatic as those resulting from the administration of androgens, but some may force the cessation of treatment.[90] Nausea and anorexia are regularly noted during the first two or three weeks of therapy. These symptoms usually subside spontaneously, but in some cases the patient may be entirely intolerant to the hormone. On occasion, another preparation may be better tolerated. Engorgement of the breasts and tenderness of the nipples are prominent early effects, particularly in younger women. Deep pigmentation of the nipple and areola and often the axilla and of scars, as in pregnancy, is common. Some workers[101] believe that the presence of such pigmentation is a harbinger of a favorable response. We have seen pigmentation without an accompanying satisfactory clinical result. Conversely, some lesions may regress without concomitant pigmentation, although absence of pigmentation is much commoner in unresponsive lesions. A "rejuvenation" of the skin with increased turgor may be seen. Uterine bleeding is frequent but is seldom severe enough to require dilatation and curettage. It is especially noted on withdrawal of estrogen but may occur during treatment. A correlation of the frequency of uterine bleeding with the patient's age rather than with the dosage has been suggested by Walpole and Paterson,[99] who found bleeding commoner in patients over sixty and considered this to be a real basis for the clinical impression that estrogens are more effective in older patients. Our findings suggest that duration of treatment as well as dose level may be responsible for uterine bleeding. More-

over, bleeding was less frequent in the older age group.

One of the most distressing symptoms we have noted is incontinence, usually of the stress type. This, coupled with the frequency and urgency that are prominent side-effects may be a source of intolerable discomfort. It may be related to an alteration in tone of the pelvic musculature.[98] Fluid retention is common and may precipitate cardiac decompensation in patients with compromised cardiac function. This can be avoided or controlled by the usual cardiac measures, including diuretics. Hypercalcemia may occur early in estrogen administration, although less often than with androgens. Changes in calcium, phosphorus and alkaline phosphatase identical with those noted with androgens occur in patients with osseous metastases responding to estrogens.

Considerable attention has been focused on changes in the vaginal smear during estrogen administration. Walpole and Paterson[99] noted that patients who show a high "smear response" (pronounced estrogen effect) may or may not respond to therapy whereas those who show no vaginal response rarely display significant clinical improvement. They were impressed by the almost complete absence of vaginal response in certain patients receiving high doses of estrogens; they are currently studying this phenomenon by means of intravaginally administered stilbestrol. Cutler and others[96] found that changes in the vaginal mucosa occur in nearly every case, regardless of clinical response.

Although estrogen administration is efficacious in certain cases of cancer of the female breast, there have been reports of the development of bilateral cancer of the breast in males receiving large doses of stilbestrol for carcinoma of the prostate.[103, 104] Campbell and Cummins[105] have recently reviewed several such reported cases, adding another of their own; by utilizing histochemical methods to demonstrate acid phosphatase they have found good evidence that the breast lesions in their case were metastatic from the prostate carcinoma. Two similar cases of probable prostatic origin have been described.[106, 107] These authors and Stewart,[108] who has reviewed some of these cases, believe that such mammary lesions are most probably of prostatic origin.

McClure and Higgins[109] have recently described a case of carcinoma of the bladder in a male treated with estrogen in whom bilateral carcinoma of the breast developed with pathologic features quite unlike that of the primary bladder tumor. This was considered an undifferentiated carcinoma simplex of the male breast.

Duration of Hormonal Therapy

Since evidence of objective response to androgens and estrogens may take some weeks, it is apparent that a trial of three months of therapy should be allowed before resorting to other methods of treatment. Hormonal therapy should be discontinued immediately if there is evidence of accelerated growth beyond that anticipated in the natural course of the disease or if serious complications occur. If beneficial effects are observed, two general plans of therapy may be followed.[9, 24]

The first plan is that of interrupted or limited treatment. Treatment is maintained as long as regression proceeds but is discontinued when the disease process apparently becomes inactive. Such an inactive status may persist for a considerable period after withdrawal of the hormones. This regimen is based on the assumption that the residual disease represents the least susceptible cells and that they may easily become adapted to the environment created by longer periods of therapy. It is further assumed that reactivation may be treated again with expectation of another favorable response. This potentiality has been verified in some cases.

The second procedure is that of continuous treatment after the disease has undergone apparently maximum regression and remains stationary. This plan is based on the premise that the more susceptible cells will be affected first and that a longer period of therapy is necessary to influence the more resistant cells. The growth capacities of the latter cells may thus be partially held in check for a longer interval, even though they eventually escape the influence and may assume even greater activity than they possessed at the outset.

With either method, reactivation is inevitable; it has not yet been established which is more efficacious in postponing the recrudescence. Each plan has its proponents. Thus, because of observations that patients may continue to improve after cessation of therapy, with protracted therapy thus apparently made unnecessary, courses of treatment of definite length or total dosage are advocated by some.[36, 47, 64, 71, 72, 94, 95, 99] On the other hand, because they observed rapid deterioration on cessation of initial courses of therapy in some patients, a number of observers consider it inadvisable to withdraw treatment. They continue it indefinitely at the same dosage or with a so-called maintenance dosage at lower levels.[42, 53, 60, 97, 98]

In some cases, when relapse occurs on either androgen or estrogen therapy, a change to the opposite hormone may produce another remission. Likewise, withdrawal of all therapy during a period of reactivation may sometimes be followed by a remission.

Mechanism of Action of Hormone Therapy of Breast Cancer

It is an amazing physiologic phenomenon that the withdrawal of estrogens by castration, their inactivation with testosterone or their administration after the titer has spontaneously waned with the menopause should, in certain cases, lead to marked regres-

sion of advanced carcinoma of the breast. The mechanism of the production of the usual "side-effects" and the general increase in well-being that often accompanies the administration of androgens and estrogens is quite readily explained by the inherent characteristics of the sex hormones, but their use as specific agents against breast cancer remains empirical. Why should their administration produce profound alterations in mammary carcinoma and its metastases in only some cases? Why is not this favorable effect more constant and predictable in patients who appear to be clinically and pathologically similar? Why is it that lesions undergo profound regressions in one site while new disease develops or existing processes progress at another? Why is reactivation of the cancer, either locally or at a distance, inevitable even after a most dramatic initial response? Why do these hormones, particularly the androgens, so often relieve pain when no discernible benefit accrues to the carcinomatous lesions themselves? The answers to these questions are elusive, although the literature abounds in theories attempting to correlate these effects with the known or postulated actions of these hormones.

Even though the precise mechanisms cannot be defined, present evidence suggests that the metabolic, carcinogenic and carcinolytic potentialities of the hormones at any given time are dependent on the coincident physiologic status of the host. Certain possibilities that may explain some of the observed phenomena have recently been presented and may be summarized here.[110]

One possibility is that the benefits of castration may result from estrogen deprivation or from a relative increase in androgenic or other hormonal activity. Although moderate dosage of estrogens may accelerate the growth of breast cancer in premenopausal women, very large doses that produce amenorrhea may also lead to regression.[110a] This suggests that inhibition of pituitary gonadotropic factors may play a role. Some authors assign the major role of estrogen effect to alteration of pituitary factors.[49, 62]

Previous artificial or natural menopause renders lesions similarly susceptible to estrogen administration, perhaps through a change in the physiologic status of the host. The effect of estrogens on osseous metastases in postmenopausal women, which is similar to androgen response in women of any age, suggests that the mechanisms by which this occurs may be somewhat different with the two types of hormones. It is possible that the estrogen has its major effect on the disease in the bone and that calcification and apparent osteogenesis may occur only after regression of the disease. Another possibility is that estrogens have a dual effect by simultaneously acting on the disease and stimulating calcification and osteogenesis, of which they are capable. It is our impression that the objective responses in bone and the metabolic and hemopoietic effect induced by estrogens, although qualitatively similar to those induced by castration or by androgens, occur more slowly. Thus, it is possible that the major effects of estrogens are on the neoplastic process with secondary metabolic responses and that castration and androgenic effects may be primarily metabolic in origin.

Another possibility is indicated by the fact that the administration of sufficient amounts of androgens to premenopausal women leads to clinical effects similar to those seen after castration. The effects may in part again be attributed to inhibition of pituitary gonadotropic activity, thus leading to suppression of ovarian function. If elimination of estrogenic activity is the sole factor, this may occur in the circulation or at the tissue level. However, the role of androgens in protein synthesis and osteogenesis must also be taken into consideration. Androgens conduce to protein formation either by stimulation of anabolism or by inhibition of catabolic processes. This capacity is also probably related to bone formation. These latter factors in themselves may produce beneficial systemic effects without necessarily influencing the tumor. Moreover, these same capacities may account to a great extent for the objective responses in metastatic osseous lesions, whereby tumor growth may be handicapped by increased bone formation without direct effect on the tumor. These theses are supported by the wide discrepancy between the subjective and objective responses to androgen therapy. In fact, in some cases the disease may be accelerated in spite of general systemic improvement. This raises many questions. The administration of testosterone to postmenopausal or castrated women sometimes results in an increased urinary excretion of estrogens.[80] This suggests that, under some circumstances, at least, androgens are involved in increased estrogen production; this might help to explain the favorable effects on soft-tissue breast lesions occasionally seen in postmenopausal women. Although other and equally important factors are undoubtedly involved, the known physiologic properties of the androgens appear to be actively contributing to the observed effects on breast cancer.

Certain workers attribute the entire action of androgens in cancer to their effects on calcium metabolism, alkaline-phosphatase stimulation and osteoblastic activity. This is challenged by Sylvén and Hallberg,[53] who postulate a central-nervous-system effect of androgen that might alter the pain threshold and thus relieve bone pain.

It can be theorized that castration and estrogen and androgen administration under certain circumstances enhance an inherent defense reaction that in itself is not capable of reversing the course of a progressive breast cancer. Evidence in favor of this thesis is seen in cases in which regression of the lesion continues when treatment is discontinued before the maximal response has been obtained.

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The invariable reactivation of the lesions after a favorable response suggests an adaptation of the more resistant cells to an environment originally rendered unfavorable to tumor growth. Some of these lesions may again regress when all hormone therapy is withdrawn or when a new type of hormone therapy is instituted, suggesting that such lesions are still vulnerable to alterations in the physiologic or metabolic status of the host and that they are not completely autonomous.

Recent observations suggest that the adrenal gland plays a vital role in the response of breast cancer to hormonal alteration. Experiments by Faloon, Gorham and others[111] raise the possibility that testosterone may operate by inhibiting the normal pituitary-adrenocortical mechanism. In a small series of cases, the eosinophil response to epinephrine before and during testosterone treatment has been followed. Less than the usual response appears to be correlated with a favorable clinical effect.

Intensive studies of steroid metabolism and excretion in cancer patients before and during hormonal therapy are being pursued.[80, 88, 112-118] These investigations require much time; as a result, sufficient time has not elapsed to permit significant conclusions. Nevertheless, Dobriner and his associates[112,117] have found steroid compounds in the urine of patients with cancer and sometimes in that of patients with adrenal hyperplasia and hypertension that are not found in normal controls. On the basis of these findings they have postulated that these compounds may arise in the adrenal gland and that the adrenal response is altered primarily or as a result of neoplastic disease.

Nathanson and his co-workers[80] have found significant variations in excretion patterns of four major steroid complexes in patients with cancer and other diseases subjected to treatment with ACTH or steroid hormones. Although no generalizations may be made from the study of a relatively small series of cases, the data suggest expansion of this aspect of the problem.

A logical place in which to seek the key to the response of tumor tissue to major shifts in the hormonal balance of the host is at the cellular level. Extensive pathological and histochemical studies of malignant and normal tissue removed surgically or at autopsy from hormone-treated patients have been undertaken.[17, 66, 93, 119-124] It has been suggested that the histologic alterations occur not primarily in the tumor cells but in the supporting stroma. This is based on the observation that the tumor appears to be gradually replaced by fibrous tissue, within which isolated nests of viable cancer cells are nearly always demonstrable.[123] Sirtori and Grattarola[93] claim that there is a histologic difference in the response to estrogen in premenopausal and postmenopausal women. In the former a large number of fibrillas develop, and the connective tissue appears soft; in older women a fibrous, hard stroma develops that is much poorer in cells. Necrosis of tumor cells often accompanies the fibrous proliferation, with collections of plasma cells and lymphocytes frequently found near the necrotic foci.[123] It is held by some workers that necrosis of cells is the primary effect and that stromal changes are a normal response to tissue death. Thus this aspect, although probably difficult of solution, needs further investigation.

Chemical studies of proliferating stroma reveal an increase in alkaline phosphatase activity and in high-polymer sulfuric-acid esters.[120] The distribution of free amino acids in normal and malignant tissues taken from patients under hormone therapy is being investigated by Awapora and Henderson[56] by chromatographic technics.

It is generally agreed by all who have made clinical and pathological studies that relatively slowly growing tumors respond best to hormone therapy. Histologically, however, it is difficult to ascribe a specific appearance of the tumor to a definite type of response to hormones.

Conclusions

A review of the present status of hormone therapy in breast carcinoma might most fittingly be concluded by a quotation from the Subcommittee on Steroids and Cancer of the Committee on Research.[55]

> There is now available for the treatment of breast cancer a third weapon in the form of steroid hormones.
>
> Barring future developments, this weapon will prove useful in the treatment of those patients with extensive and distant lesions who, heretofore, have been beyond direct attack on the disease.
>
> Surgical treatment and irradiation, singly or in combination, still must be considered the primary forms of treatment, steroid hormone therapy being reserved only for those cases in which orthodox methods cannot be applied or have proved unsuccessful.

Specific indications for use of these methods according to present knowledge are as follows:

Castration. This is primarily beneficial in premenopausal patients with disabling symptoms, particularly those with osseous or pulmonary metastases. It is occasionally of value in women just past the menopause. Present evidence suggests that it is better to withhold the procedure until ominous signs occur, in the hope that a longer respite may be obtained.[24]

Androgens. These are indicated as palliative agents in women regardless of age, particularly in the presence of pain and weakness secondary to osseous metastases. These effects are apparently more easily elicited in premenopausal patients but in these cases castration appears to have a distinct advantage.

Estrogens. These should be reserved for patients who are at least five years beyond the menopause (either spontaneous or induced). Their use is sometimes indicated in other patients when other measures have been exhausted. They are of greatest

benefit in the palliative management of primary lesions and soft-tissue metastases, but osseous lesions may also respond favorably.

(*To be concluded*)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38041

PRESENTATION OF CASE

First admission. A sixty-five-year-old woman entered the hospital because of right-chest pain.

Six months before entry the patient developed "neuritis" in the hands, right shoulder and legs, followed by increasing tiredness, anorexia and weight loss. One month before admission she had an attack of right-upper-quadrant pain without nausea; this was severe enough to require an injection by her physician for relief. Three weeks before entry she developed pain and swelling of the right calf. Two weeks before admission she noted constant right-lateral-chest pain that was aggravated by deep breathing and that became much more severe two days before admission. For the week before entry she had a slight unproductive cough and night sweats concomitant with the taking of aspirin. There was a total weight loss of 28 pounds over the six-month period preceding admission.

On physical examination there was marked splinting of the right chest but no tenderness on palpation. There was slight dullness and decreased breath sounds in the right axilla but no rales or rub. There was a soft mitral systolic murmur. The abdomen could not be relaxed enough for a proper examination. There was no swelling or tenderness in the extremities.

The temperature was 98.0°F., the pulse 80 and the respirations 25. The blood pressure was 110 systolic, 70 diastolic.

The urine gave a ++ reaction for albumin. Examination of the blood revealed a white-cell count of 13,300, with a normal differential, and a hemoglobin of 13.6 gm. The nonprotein nitrogen was 22 mg., the fasting blood sugar 88 mg., the total protein 6.1 gm. and the cholesterol 255 mg. per 100 cc.; the sodium was 136.9 milliequiv., the chloride 99 milliequiv. and the potassium 4.9 milliequiv. per liter. Cytologic examination of the sputum for malignant cells was negative on one specimen and doubtful on another. Roentgenograms of the chest showed the right lower lobe to be decreased in size and to contain a number of discrete linear areas. There was a small amount of fluid in the left costophrenic angle. A gastrointestinal series and an intravenous pyelogram were negative. A Graham test showed a normally functioning gall bladder containing stones. A barium-enema examination showed diverticula of the sigmoid, and descending and transverse colon.

The patient improved gradually, with lessening of the chest pain and marked clearing on x-ray examination of the process at the right lung base. On the twenty-eighth day she developed discomfort in the left thigh and groin that prevented her from walking. There was no calf tenderness and Homans' sign was negative, but there was slight tenderness along the left saphenous vein, and there was a tender lump 2 cm. in diameter, just below the inguinal ligament, medial to the femoral artery. Dicumarol therapy was begun and there was improvement by the following day. Later on this day, after dinner, she had the sudden onset of severe crampy right-upper-quadrant pain that radiated through to the base of the scapula. She was nauseated and vomited, with relief of the severe pain but persistence of a localized right-upper-quadrant pain. There were no masses or definite tenderness in the abdomen. The temperature was 99.6°F. and the pulse 120. The white-cell count was 18,900, with 81 per cent neutrophils. The urine was negative. The serum amylase was 130 units per 100 cc. On the thirty-second day the pain had decreased markedly, the temperature was normal and the white-cell count was 61,200. On the thirty-seventh day the patient passed 2 homogeneous tarry stools; these gave a ++++ guaiac reaction. The prothrombin time was 63 seconds (normal, 17 seconds), the white-cell count 40,000 and the hemoglobin 12 gm. The dicumarol was stopped and Hykinone was started. On the thirty-ninth day the stools became brown, and the patient had improved generally; the pain occurred only occasionally and her appetite was better. The prothrombin time remained below 10 per cent for nine days in spite of Hykinone therapy. The serum protein was 5.72 gm. per 100 cc. with an albumin-globulin ratio of 0.6. The bromsulfalein test, cephalin flocculation, thymol turbidity and nonprotein nitrogen were normal. She improved steadily and was discharged on the fifty-second day. A few days prior to discharge the prothrombin time was 24 seconds (normal, 17 seconds), the white-cell count 13,000 and the hemoglobin 12.0 gm.

Second admission (two weeks later). In the interval the patient had only occasional mild abdominal pain, felt well generally and gained strength. Physical examination revealed a tender mass in the epigastrium in the region of the head of the pancreas. The left leg was slightly swollen but not tender.

The temperature was 99.6°F., the pulse 90 and the respirations 24.

The white-cell count was 28,700 per cu. mm. and the hemoglobin 12.6 gm. The urine had a specific gravity of 1.024 and gave a ++++ reaction for albumin. A stool guaiac reaction was negative. The prothrombin time was 21 seconds (normal, 17 seconds). The total protein was 6.07 gm., the albumin 2.55 gm. and the globulin 3.52 gm. per 100 cc.

A cholecystectomy and choledochostomy were performed. At the time of operation the head of the pancreas was felt to be enlarged and indurated. A postoperative cholangiogram showed easy filling of the common duct and radicles but only a small quantity of contrast substance in the duodenum. No definite stone or filling defect was seen. Her convalescence was uneventful and she was discharged on the twenty-eighth day.

Final admission (six weeks later). For the first three weeks after discharge the patient's appetite was good, and she regained her strength. However, about three weeks before admission she began to vomit persistently and was unable to retain solid foods. She had occasional episodes of crampy abdominal pain associated with the nausea and vomiting and an occasional attack of diarrhea. Progressive swelling of the legs and abdomen developed. She became increasingly drowsy. Her appetite was almost nonexistent and she was losing weight.

On physical examination the tongue was smooth and red, with atrophic papillae. The diaphragms were high bilaterally. There was decreased resonance and breath sounds at the right base. The heart was enlarged to the anterior axillary line. The abdomen was distended and a fluid wave was present. There was +++ edema extending from the feet to the thoracic region.

The temperature was 97.8°F., the pulse 80 and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis showed a specific gravity of 1.020 and a +++ reaction for albumin; the sediment contained 15 white cells per high-power field and frequent hyaline casts. A twenty-four-hour specimen of urine contained 0.15 gm. of albumin per 100 cc. The white-cell count was 9000 per cu. mm. and the hemoglobin 14.6 gm. The sodium was 131 milliequiv., the chloride 87 milliequiv., the carbon dioxide 24.0 milliequiv. and the potassium 4.4 milliequiv. per liter; the cholesterol was 179 mg., the nonprotein nitrogen 21 mg. and the total protein 5.8 gm. per 100 cc. with an albumin-globulin ratio of 0.7. The serum calcium was 6.8 mg., the phosphorus 2.7 mg., the alkaline phosphatase 4.4 units, the serum amylase 25 units and the bilirubin less than 0.2 mg. per 100 cc. indirect and total. The bromsulfalein test and cephalin flocculation were negative. A phenolsulfonphthalein test showed 45 per cent excretion in one hour and 70 per cent in two hours. Examination of the stools showed them to be soft, formed and mustard yellow; they were guaiac negative and contained no muscle fiber, no neutral fats and a moderately increased amount of fatty acids and soaps. Paracentesis yielded 150 cc. of milky yellowish fluid with a specific gravity of 1.007, and a smear stained with Sudan III showed the fluid to be filled with fat droplets. It contained 1.8 gm. of protein per 100 cc. A cytologic smear was negative for tumor cells.

The patient was treated symptomatically with a low-salt diet, pancreatic extract and intravenous albumin. Her condition remained unchanged. On the sixteenth day a paracentesis yielded 4610 cc. of milky yellowish fluid with a specific gravity of 1.010. The total protein of this fluid was 2.76 gm. and the total lipid content was 580 mg. per 100 cc. At that time the serum sodium was 124.2 milliequiv., the chloride 82 milliequiv., the carbon dioxide 27.0 milliequiv. and the potassium 3.7 milliequiv. per liter; the albumin was 2.89 gm. and the globulin 2.09 gm. per 100 cc. One month after admission there was very little change; the abdomen was distended and tympanitic and the edema persisted. The patient had become increasingly listless and was unable to retain much taken by mouth. An x-ray film of the abdomen showed considerable gas in the abdomen with dilated loops of small bowel. She developed dyspnea and polyuria; the urine contained 15 white cells per high-power field and numerous bacteria. Catheterization showed considerable residual urine and she was treated with irrigations and Gantrisin. In spite of attempts to maintain the electrolyte balance by gastric-tube feeding the patient continued to fail and died on the thirty-second day. Two days before death the serum sodium was 98.7 milliequiv. and the chloride 67 milliequiv. per liter; the albumin was 2.47 gm., the globulin 2.30 gm. and the nonprotein nitrogen 17 mg. per 100 cc.

Differential Diagnosis

Dr. Myles P. Baker*: The important features at the time of this woman's first admission to the hospital were these: weight loss of 28 pounds, right-upper-abdominal pain followed by pain and swelling in the right calf and then right-lateral-chest pain. This picture, taken together with the physical findings, would certainly make me first consider thrombophlebitis in the leg, with pulmonary embolization and infarction. I think we might look at the x-ray examination of the chest now, Dr. Hanelin.

Dr. Joseph Hanelin: At the time of the first admission, as described in the protocol, there is evidence of partial collapse of the right lower lobe and linear streaking within it. About two weeks later the chest has cleared and the lungs at this time appear to be normal. The heart is enlarged in the region of the left ventricle.

*Physician, Massachusetts General Hospital.

DR. BAKER: She seemed to be improving for these first four weeks of the hospital stay, and it was presumably during that time that x-ray studies revealed these diverticula of the sigmoid and gallstones in a gall bladder that appeared to be functioning normally. On the twenty-eighth day things began to go wrong and the patient developed pain in the left thigh, which was apparently considered compatible with a new onset of thrombophlebitis. On the same day she developed severe right-upper-abdominal pain associated with fever and a pulse rate perhaps a little faster than one would expect, leukocytosis and a really elevated serum amylase. It is interesting to note that on this occasion albumin was not found in the urine.

DR. BENJAMIN CASTLEMAN: That is an error; it also showed ++ albumin.

DR. BAKER: Then she continued to show albumin in the urine.

This severe right-upper-quadrant pain seems to have relented rather quickly, within four days. I do not know how long the temperature lasted. There was a notable leukocytosis associated with this pain. Subsequently the appearance of tarry stools was coincidental with a finding of a prolonged prothrombin time and may have been due to this. It seems to have been a passing phase.

The first question here about the nature of this pain would seem to be this: Was the pain associated with gallstones in the cystic duct, with edema of the pancreas or with an acute pancreatitis? The elevation of the serum amylase is important. Serial determinations of blood amylase are much more revealing than a single determination, but with a high normal level of 45 to 50 units an elevation of 130 units means acute pancreatitis in the presence of severe pain, always with the reservation in mind that there may be high levels of pancreatic ferments in the blood in cases of intestinal obstruction and perforated peptic ulcer. The levels of serum amylase and lipase in these latter two abdominal emergencies are not as high as they are in the presence of acute pancreatitis. I think our attention is drawn to the definite probability that she had acute pancreatitis.

The important feature in the second admission, — which I presume had already been arranged when she left the hospital, with cholecystectomy in mind, — was a tender epigastric mass in the region of the head of the pancreas, which I must say is not a very likely physical finding in either chronic pancreatitis or carcinoma of the head of the pancreas. The left leg was slightly swollen — possibly a bit of evidence in favor of her having had a femoral thrombophlebitis a few weeks previously, during the first admission. Again fever was present, the leukocytosis persisted and a ++++ albumin in the urine was noted, up to that point unexplained. There was no occult blood in the stool. The prothrombin time continued slightly prolonged. Again there was a real hypoalbuminemia, which I have not explained on the basis of pulmonary embolization or infarcts plus one attack of acute pancreatitis. It suggests to me that the patient had been seriously ill with an occult disease for a longer time than the nine weeks that passed since the first admission to the hospital. The cholecystectomy and common-duct drainage were performed, and at the time of operation the head of the pancreas was found to be hard and indurated. Was a biopsy done, Dr. Castleman?

DR. CASTLEMAN: No.

DR. BAKER: After the operation cholangiograms were done and seemed to indicate some delay of contrast substance entering the duodenum, which might well have been produced by a chronic inflammatory or neoplastic process in the head of the pancreas. There was only partial obstruction. Six weeks later she re-entered, very much the worse for wear, with physical findings as noted, particularly ascites, and edema from the feet to the chest. The high diaphragms and displacement of the heart to the left were probably associated with the ascitic distention.

Several laboratory data call for comment. There was a definite reduction in the serum amylase level, with the finding of only 25 units on this admission. I think that is not incompatible with the presence of extensive pancreatic disease at this time. If she had a cancer of the pancreas, there may well have been enough progressive destruction of pancreatic tissue in the course of these eight or more weeks to have made it impossible for persistent pancreatic-duct obstruction to produce high serum-amylase levels in the blood. As may often be the case, one would be confused by a normal blood amylase if this were the first hospital admission and would say that there was no pancreatic disease. In cases of carcinoma of the pancreas a normal blood amylase or blood lipase is not infrequent if the patient is far along in the course of the disease. Secondly, the serum-calcium figure was unexpectedly low — 6.8 mg. Could this have been due to mobilization of blood calcium to combine with fatty acids produced in the neighborhood of a diseased pancreas by pancreatic lipase acting on surrounding fatty tissue? That has been reported in acute pancreatitis.[1] The significance of the reduction of the serum calcium must have been modified by the low level of serum albumin. But the level of 6.8 mg. seems to be lower than I would expect were I dealing simply with a reduction of serum calcium associated with a decrease in serum albumin to about 2.5 to 2.7 gm. per 100 cc. This hypocalcemia does make me wonder about the possibility of severe pancreatic damage and fat necrosis around the pancreatic border. Thirdly, the persistent albuminuria led to studies of kidney function. The phenolsulfonphthalein excretion seems to have been fairly good. The finding of only 1.5 gm. per liter of albumin would seem to

be too low a figure for me to regard the proteinuria as indicative of a nephrotic glomerular nephritis.

DR. DANIEL ELLIS: I do not think that is a correct figure, Dr. Baker. It was difficult to collect the specimen on the ward.

DR. BAKER: I had thought that this patient was not putting out enough albumin and not losing enough protein in the urine to account for the low serum albumin.

DR. ELLIS: She had repeated urinalyses, and the albumin was always ++ to ++++ during all the hospital admissions.

DR. BAKER: To proceed to other laboratory data, what shall I make of this milky yellowish ascitic fluid? Strictly, I suppose, on the data given here this was a chyliform ascites rather than a true chylous ascites, as the protein value, — under 3 gm., — was rather low for true chylous ascites.

The attempts at treatment directed at minimizing pancreatic insufficiency were futile, and the patient continued to deteriorate, with ante-mortem electrolyte levels that indicate the inefficacy of what must have been intensive treatment. It seems to me that most of the facts given here are consistent with a diagnosis of carcinoma of the pancreas. These facts are worthy of note: She had, I gather from the data, thrombophlebitis. This is a manifestation not infrequently seen in cancer of the pancreas. In some 30 per cent of such cases in one series[2] involving the head and body of the pancreas, multiple venous thromboses were found. The finding of a high serum amylase I have already discussed, and the possible significance of a normal serum amylase on the third admission has been mentioned. There were no serum-lipase studies; lipase is notably more indolent in its rise and remains higher longer in cancer of the pancreas than does the serum amylase. Ascites is not uncommon in cancer of the body of the pancreas; in one series reported by Duff[3] at Johns Hopkins ascites was found in 10 out of 16 cases, and in none of them was the ascitic fluid bloody. In none of the cases of cancer of the body of the pancreas was the ascitic fluid of a chylous character, but chylous ascites has been reported in association with cancer of the body of the pancreas, presumably due to involvement of the lymphatics and actual rupture of the receptaculum chyli of the lower thoracic duct. The absence of jaundice would not bother me in making such a diagnosis, for from what I have read of cancer of the pancreas[4] painless jaundice occurs in only 15 to 25 per cent of cases and may be absent in 20 to 25 per cent of the cases restricted to the head of the pancreas. The possibility that this patient had more kidney disease than I have taken into account remains, but I do not see that I have the data to back up such a diagnosis. The presence of albuminuria of the degree described in this protocol I would consider compatible with pressure of involved metastatic lymph nodes on renal veins; lymph-borne metastases from such a tumor as I have predicated are commonly retroperitoneal and might easily produce such obstruction.

DR. CASTLEMAN: Dr. Adams, you saw this patient; would you like to comment?

DR. F. DENNETTE ADAMS: Several consultants saw this patient. I do not believe any two of them agreed on the diagnosis. My line of reasoning was similar to Dr. Baker's. I put emphasis on the facts that the patient presumably had some intra-abdominal disease, probably malignant, and that before abdominal symptoms appeared she had an attack of thrombophlebitis. Her loss of weight was rapid. Because rapid loss of weight and thrombophlebitis are so common in cancer of the pancreas, I committed myself to that diagnosis.

DR. ELLIS: I saw this patient during her third admission. In looking over her record, I was impressed by the fact that she consistently had albuminuria, a low specific gravity and a low serum albumin. When she re-entered, in addition to the other findings she had developed ascites. It was apparent that she had absolutely refused to eat anything while she was in the convalescent home. She did not improve after she came into the hospital. We were unable to feed her by mouth, so we used a tube. She promptly vomited everything that we put in, to the point that she aspirated some, and we had to reduce the tube feedings. It is not mentioned in the protocol, but toward the end she began to have almost constant profuse diarrhea — yellow watery fecal material in the bed all day long.

On the strength of Dr. Leland McKittrick's opinion, — that he did not believe that this patient had cancer when he explored her, — we tried to control those disturbances. I decided that she had chronic renal disease, chronic pancreatitis and poor nutritional intake and that these three were actually the conditions that were playing a part in the formation of the ascites and low serum protein and that later led to the electrolyte imbalance, nausea, vomiting and diarrhea. I held to that to the end, well knowing that she might have had cancer of the pancreas.

DR. EDWARD B. BENEDICT: I have seen chylous ascites in many cases of lymphoma. Was that considered?

DR. ELLIS: All types of cancer were considered. We believed that she could have lymphoma, but we had no proof that she did. Other causes of chylous ascites were also considered. We have seen what appeared to be chylous ascites in mesenteric thrombosis; we have sometimes seen it in cirrhosis. We tried hard to pin a diagnosis of cirrhosis on this patient because of the persistent low albumin, but with a normal flocculation test and a bromsulfalein test of only 8 per cent we did not have sufficient evidence for making such a diagnosis. Dr. McKittrick made no comment in his operative note on the ap-

pearance of the liver, but he told me that at the time of operation it looked normal.

DR. BAKER: I meant to mention the possibility of liver disease, but, as Dr. Ellis has said, it seems to be ruled out by the repeated bromsulfalein tests.

DR. ELLIS: I do not know what Dr. Castleman has up his sleeve. I have been trying to find out what the patient had. I was there at the autopsy, and I did not know what she had when I left the post-mortem room. She did not have chylous ascites then; she had clear ascitic fluid.

DR. CASTLEMAN: Have you any comment, Dr. Aub?

DR. JOSEPH C. AUB: I think I had better not say anything. I had an idea before Dr. Ellis made his last remark.

CLINICAL DIAGNOSES

Chronic renal disease.
Chronic pancreatitis.
Malnutrition.

DR. BAKER'S DIAGNOSIS

Carcinoma of head and body of pancreas.

ANATOMICAL DIAGNOSIS

Primary amyloidosis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy, as Dr. Ellis has mentioned, we did not know exactly what the patient had. We were quite sure that she did not have a carcinoma of the pancreas from the gross appearance of the pancreas. It was firm, but as we cut through it we found normal lobulation in most areas. In the region of the head there were areas of fat necrosis, so there had been a pancreatitis, and on microscopical section there was some evidence of a still active but mild pancreatitis. Most of the pancreas, however, seemed to be normal, and the small amount of pancreatitis probably did not contribute too much to the patient's death.

The kidneys at the time of autopsy were quite normal looking. They were not scarred, and we were hard put to explain all the marked proteinuria, the low albumin and perhaps a little increase in the globulin, if you consider that the total protein was low; I think a number of men who saw the patient thought the globulin was elevated. Microscopical sections of the kidney showed amyloidosis. Not only was there involvement of the tufts, but most of the involvement was in the walls of the arteries; almost every vessel was completely replaced by amyloid. The appearance suggested primary amyloidosis because of the fact that most of it was in the large vessels, although from the kidney alone I would not be able to decide whether this was primary or secondary amyloidosis. Seeing this slide alone in a patient with chronic pancreatitis, one might believe it was secondary amyloidosis, although I never heard of that combination. However, the only other foci of amyloid were in the walls of the medium-sized and small arteries throughout the body; none were present in the spleen, liver, sinusoids or adrenal gland, where it is usually found in secondary amyloidosis. We have here, then, an example of primary amyloidosis, which would then account for all the proteinuria and all the changes that were evident in the clinical history.

It is interesting to speculate on the etiology of the pancreatitis. It is possible that the amyloid-involved arteries in the pancreas were so fragile that a break in one of them led to a small hemorrhage, with the destruction of pancreatic parenchyma and fat necrosis. I believe the gallstones were only incidental; they did not produce any pain, and there were no stones found in the ducts. Actually, at autopsy the stones were limited to the fundus of the gall bladder. I am inclined to believe that the origin of the pancreatitis may have been on the basis of amyloidosis. Dr. McKittrick made an interesting note, — going back to the operative report, — "A muscle-splitting incision was made. The muscle was pale and weak looking" — which probably indicated amyloid involvement of the muscles. The lungs showed a lot of amyloid, which would be in keeping with primary amyloidosis; lung involvement is rarely seen with the secondary form of amyloidosis. After having made this diagnosis from the autopsy, I went back and looked at the sections of the gall bladder from the cholecystectomy, and there it was; we had completely missed the amyloid in the wall of the gall bladder. It was a very thin-walled gall bladder and was all stained pink — not only the amyloid but the surrounding tissue; knowing she had it, it is obvious now.

DR. BAKER: Did she have thrombophlebitis?

DR. CASTLEMAN: I do not believe we have a note about the vessels; we did find thrombi in the lungs and some healed infarcts.

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CASE 38042

Presentation of Case

A sixty-two-year-old man entered the hospital because of dyspnea.

Twelve hours prior to admission, while at rest, he had a sudden, sharp, severe pain in the left interscapular region that subsided within five minutes. After this he broke out in a cold sweat and became quite short of breath. He went to bed, but dyspnea persisted although he had no pain. In the morning his physician noted that during the twelve-hour period the blood pressure had dropped and the pulse rate had risen. There was no fever, chills, cough, hemoptysis or leg pain. Since the onset of the pain he had not passed urine or had a bowel movement.

A subtotal gastrectomy had been performed eleven years previously for peptic ulcer. There had been no other serious illnesses or operations. He had never before had dyspnea, orthopnea, chest pain, cough or edema.

Physical examination revealed a drowsy, pale, dyspneic man who was obviously acutely ill and was complaining of diffuse abdominal soreness. The neck veins were flat. The nails were cyanotic. The lungs were clear. The heart was not enlarged to percussion and the rhythm was regular, although the sounds were very faint. There were no thrills or murmurs. The abdomen was diffusely distended and tender, without point tenderness, spasm or rigidity. No organs or masses were palpable. There was no fluid wave or shifting dullness. The peripheral pulses were not palpable. There was no peripheral edema and no tenderness in the calves; Homans' sign was not present. Neurologic examination was negative except for the absence of deep tendon and corneal reflexes.

The temperature was 98.4°F., the cardiac rate 140 and the respirations 68. The blood pressure was unobtainable.

Four cc. of urine was obtained by catheter; this was normal. Examination of the blood revealed a hemoglobin of 11.5 gm. and a white-cell count of 25,000, with 90 per cent neutrophils. A serum amylase was 6 units per 100 cc. A stool examination was guaiac negative. An electrocardiogram was normal.

There was temporary improvement after intravenous administration of norepinephrine, but despite continued therapy with this and with whole-blood transfusions the blood pressure was not obtainable. The cardiac rate slowed to 30 per minute; the patient became unresponsive and died three and a half hours after admission.

Differential Diagnosis

Dr. Edwin O. Wheeler*: This is the picture of a sixty-two-year-old man who had an illness with a very acute onset characterized by pain in the interscapular region, shortness of breath and death within fifteen and a half hours after the onset. All these point to a major cardiovascular accident of some sort, such as coronary thrombosis, massive pulmonary embolism or rupture of a dissecting aneurysm of the aorta. It is also of interest that he had no cardiovascular symptoms prior to the present illness and had been in good health. There is no recording of the patient's blood pressure. I do not believe that the old history of peptic ulcer had anything to do with the final illness. He had not had symptoms suggesting the recurrence of peptic ulcer, and the history is not a good one for perforation of a peptic ulcer.

The onset of the illness was rather sudden for coronary thrombosis, the pain becoming maximal almost immediately. The location, duration and character of the pain likewise did not suggest the pain of coronary thrombosis. Shortness of breath was a very prominent feature from the beginning to the end. One would not expect dyspnea due to coronary thrombosis to continue so long in the absence of signs of congestive failure. The anuria and the absence of peripheral pulses might be accounted for by shock in the presence of coronary thrombosis or of massive pulmonary embolism. The abdominal findings are a little difficult to account for from the standpoint of coronary thrombosis unless I assume that he had a mesenteric embolus or thrombosis. It was too soon after the onset of the illness for a mesenteric embolus but not for a mesenteric thrombosis, especially in the presence of severe shock. That might in turn account for the abdominal findings of diffuse tenderness and soreness. The

*Assistant in medicine, Massachusetts General Hospital.

strongest point against a myocardial infarct is the electrocardiogram, which was said to be negative. Is that available?

DR. EDWARD F. BLAND: Yes; it was within normal range.

DR. WHEELER: I believe the sudden onset of the illness, the character of the chest pain and the normal electrocardiogram at least twelve hours after the onset of the illness exclude coronary thrombosis as the cause of death.

Massive pulmonary embolus is another condition to consider in this sort of situation. The sudden onset is consistent with pulmonary embolus, but again the location and duration of the pain would be unusual. Most patients with massive pulmonary embolus complain of substernal pain rather than of back pain. This pain certainly was not pleuritic in nature. The dyspnea, which persisted up to the time of death, would go very well with pulmonary embolism. The patient had no cough, hemoptysis or leg pain, and on physical examination he had no signs of phlebitis, so I know of no source for a massive pulmonary embolus. The fact that the lungs were clear on physical examination would not rule out this condition, as such a finding is not uncommon early in the course of massive pulmonary embolism. Nor does the presence of a normal electrocardiogram rule it out, but an embolism massive enough to produce this clinical picture would also not uncommonly produce some abnormality in the electrocardiogram. The white-cell count of 25,000 is consistent with a pulmonary embolism or with myocardial infarction. I think pulmonary embolism is unlikely because of the location of the pain, the absence of a known source of an embolus and, possibly, the normal electrocardiogram.

Dissecting aneurysm seems to be the most likely diagnosis. The sudden onset and course, with death in a period of a few hours, are rather characteristic. Pain in the interscapular region occurs not infrequently. The pain did not radiate, as it frequently does, to the abdomen and to the legs with dissecting aneurysm. Its duration was unusually short — only four minutes, according to the record; most patients with a dissecting aneurysm have pain lasting longer than that. However, we have seen patients in whom no history of pain could be established. Dyspnea is almost universal during the acute period of a dissecting aneurysm. As we know, the symptoms vary considerably, due to the fact that a number of different vessels may be occluded with the dissection of the aorta. Thus it is very common to note abdominal symptoms due to occlusion of the renal artery, either by the dissection itself or by secondary thrombosis. I would not, however, expect an occlusion of all four peripheral pulses. Pulses were missing in the arms and legs. The absence of pulses in one or two extremities is common, but it would be unusual in all four extremities on the basis of occlusion of the vessels. The severe state of shock that the patient was in would more likely account for the absence of pulses. The neurologic findings may vary considerably due to infarction of the spinal cord at various levels and necrosis of peripheral nerves due to occlusion of the blood supply. Absent deep tendon reflexes are commonly found in patients with dissecting aneurysms. The findings in regard to the heart are not particularly disturbing. Nearly all patients with dissecting aneurysm have preceding hypertension and usually some hypertensive heart disease. This might not be noted at physical examination. Murmurs occur not uncommonly, but none were heard in this case. A prompt fall in hemoglobin usually occurs with dissecting aneurysm, and a white-cell count of this degree is very common. There is one thing that bothers me, however; that is the finding of a normal electrocardiogram. In all the cases reported by White[1] and by Levinson and others[2] from the Los Angeles County Hospital there were some abnormalities — evidence of previous coronary disease, left-ventricular hypertrophy or an abnormal finding of no particular pattern.

In conclusion, I shall make the diagnosis of dissecting aneurysm of the aorta. The terminal episode suggests complete heart block; the heart rate slowed to 30 per minute. This has been reported in patients whose dissection included the interauricular septum. That might possibly have occurred in this case. One would think the terminal episode might have been a cardiac tamponade with a dissection into the pleural cavity. Occasionally the aneurysm ruptures into the right ventricle.[3] I do not think I am given enough information to be certain about the terminal episode. He may also have shown left-ventricular hypertrophy due to hypertension.

DR. BLAND: This was one of those desperate Emergency Ward situations in which nothing seemed to alter the picture. The dyspnea was out

of all proportion to any diagnosis we could make. That is why we favored the diagnosis of pulmonary embolus although the electrocardiogram was not abnormal. The patient was more or less unconscious and in profound shock. He was cold and pulseless, and on one occasion his heart and respiration stopped completely; after five minutes of artificial respiration they resumed for about half an hour. We were unable to find anything abnormal in the abdomen by palpation, although he moaned and groaned, which seemed to indicate that he was in pain as well as in respiratory distress. We vacillated between dissecting aneurysm of the aorta and a massive pulmonary embolus.

Clinical Diagnosis

?Massive pulmonary embolus.
?Dissecting aneurysm of the aorta.

Dr. Wheeler's Diagnosis

Dissecting aneurysm of the aorta.

Anatomical Diagnoses

Ruptured arteriosclerotic aneurysm of the abdominal aorta.

Coronary sclerosis, severe, with arteriosclerotic aneurysm.

Pulmonary congestion and edema.

Pathological Discussion

Dr. Benjamin Castleman: The autopsy showed that the patient had neither pulmonary embolism nor a dissecting aneurysm of the aorta. This slide shows the abdominal aorta, with a large arteriosclerotic thrombus-filled aneurysm extending from a point just below the orifice of the renal artery to just above the iliac artery (Fig. 1). On the lateral border there was a tear about 3 cm. in length that had produced a massive hemorrhage into the retroperitoneal space. There must have been a slow leak at first and then a rapid exsanguination. It certainly would account for the patient's abdominal symptoms, but I do not know how that would explain the marked shortness of breath.

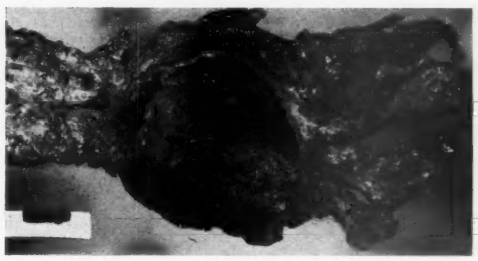

Figure 1.

Dr. Bland: Did it go upward?

Dr. Castleman: The retroperitoneal hemorrhage went upward to the level of the diaphragm; that should not produce any shortness of breath.

Dr. Bland: Nothing that we could detect encroached on the lungs; he had normal breath sounds at all times.

Dr. Castleman: He had pulmonary edema, but whether he had it all the time or not I do not know. The coronary arteries were markedly sclerotic; an interesting finding was an arteriosclerotic aneurysm of a coronary artery.

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THE "LITTLE STROKES"

Do not let me hear
Of the wisdom of old men but of their folly. . .
T. S. ELIOT

THE failures of the aging heart have become so much a part of life's present picture that another unwelcome dividend of longevity may escape attention. A slow dying at the top due to arteriosclerosis of the brain is a still more distressing organic infirmity. Especially tragic is the early descent to vegetable apathy of a giant intellect, as happened to the sage of Concord — not that it is any easier to witness in one's less distinguished patients or friends, but those degenerations seem of smaller scale.

This intimation of mortality does not refer to those normal changes in the middle-aged psyche that are functional and not organic, disturbing as they may be. These are the last of personality's growing pains — the reluctant acceptance of life's inevitable defeats, loneliness in the dwindling family circle, grudging acknowledgment of diminished stamina or a slowing urinary stream, hesitance in facing new persons or new ideas. The middle span may be painful at first. Many regrets may border on depression. The oncoming years are often contemplated with anxiety, sometimes with an exaggerated urge to save and conserve. There may be less room in the head for new names and less interest in recalling old ones. Waning sexuality may induce the I-am-as-good-as-I-ever-was-or-even-better complex and lead to embarrassing or even scandalous extramarital forays. But on the whole the waves of disenchantment, anxiousness and foreboding, a kind of inward hot flash in either sex, pass like the abdominal gas that is a usual accompaniment. Fear of cracking up or losing the mind is fairly commonly but unnecessarily entertained in the more acute phases of realizing that one is no longer young. The resourceful psyche turns conservative, husbands its energies, exercises the judgment more and the legs less, turns to raising flowers instead of children. This is euphemistically referred to as "growing old gracefully," or "being one's age." It is a result of native common sense, not of arteriosclerosis.

Slowly dying at the top is different. The subject does not seem to resent it and is usually not even aware of it. The basis of it is what Alvarez characterizes as "little bites out of the cerebral cortex," or "little strokes," due to areas of softening or thinning caused by closure of arteriolar branches. Since the motor cortex may be transiently if at all involved, there may be no outward neurologic sign of the inward state. The oldster turns night into day, gets up and dresses at 2 a.m. and finds his familiar surroundings strange. Occasional loss of sphincter control may be noted. The inertia of the old person's unvarying routine may be punctuated by petty possessiveness, tempers or unaccountable personality changes. Patriarchal carelessness in dress and susceptibility to spirits are immemorial family experiences since Noah's youngest son looked on his father's shame. Manners and ordinary social

amenities lapse. Grandpa unashamedly turns his rheumy eyes on the baby sitter's ankles and makes a small salacious joke. It is prophetic of an arbitrary change of the patient's will in favor of the night nurse after some future prostatectomy.

Electroencephalograms are not too helpful. Tests of cortical function may reveal notable gaps in memory or vocabulary or an inability to concentrate. Newer technics may soon be refined sufficiently to determine slightly diminished cerebral blood flow. Careful and sympathetic observation by a family medical adviser who is alert to the possibilities is still the best diagnostic method, but one often wishes that there were better therapeutic aids. The twice-daily walk is the simplest and most effective temporary relief of cerebral circulatory insufficiency. Vasodilators are of doubtful value. A little dextro-amphetamine by day and a mild sedative at night are often helpful. A salt-poor diet, rich in protein without too much starch or fat, is advisable. Testosterone, though sometimes effective, may activate latent malignant cells in the prostate. Comfort and guidance into snug harbor are the indications, and in this duty families and relatives must be indoctrinated.

The triumphs of medicine in coping with infant mortality and the infectious diseases have altered nature's balance and pose the seemingly greater problems of degenerative vascular disease. It is not a divinity but the mystery of arteriosclerosis that shapes the earthly endings of most lives.

THE CHANGING NATURE OF PNEUMONIA

A FEW years ago O'Hara[1] published a small volume entitled *Air-Borne Infection*. One of the interesting features of this volume, which is easily seen as one scans its pages, is a series of charts interspersed in the text, and the most striking feature of these charts is their generally uniform character. Each of these charts graphically presents the mortality rate in Massachusetts from some of the common infectious diseases, — diphtheria, measles, scarlet fever, whooping cough, pneumonia and tuberculosis, — during the first four decades of this century. They all show almost identical downward trends over the entire period, although the slope of the decline varies somewhat in some of the diseases. The charts for pneumonia, of course, show the sharp upward spike during 1918-1919, which is paralleled by the mortality curve for influenza over the same period. Most unexpected, perhaps, is the close parallel between the curves for the mortality from pneumonia and from tuberculosis over the greater part of this period, except for the spike just mentioned.

One would expect to be able to recognize on these charts the times when the progressive improvements in diagnosis, prevention and treatment became widely accepted and practiced. However, except in the case of diphtheria, there are no sharp downward dips to indicate these landmarks. Certainly it is difficult in the charts for pneumonia mortality to recognize any major effect of specific serum therapy or even of sulfonamides. To be sure, the major effect of the latter may not yet have been fully recognized by the end of the period covered by these charts. It seems likely that had these charts been extended to the present the improvements in mortality from pneumonia due to the successive introduction of effective sulfonamides and antibiotics would be readily apparent.

At the present time most internists and physicians in general practice have the impression that pneumonia has disappeared as an important disease. Those who have been in practice for a couple of decades or longer, — and particularly the men who have worked on the medical wards of large general hospitals, — can recall the significantly large numbers of cases of severe pneumonia treated throughout the winter months; they see comparatively few such cases at present.

Reimann,[2] having the same impression, undertook to obtain specific information about this matter for presentation before the American College of Physicians at its 1950 meeting. He did indeed find some definite changes in the nature of pneumonia. Most striking, perhaps, was the recognition of the nonbacterial nature of this disease in a large and increasing proportion of the number of patients with it. He learned from a number of colleagues working in several of the large hospitals throughout the country that pneumonia, including classical pneumococcal lobar pneumonia, was still frequently seen. From

South Africa he learned that the incidence of lobar pneumonia among miners in that country may actually have increased in recent years.

Most significant, however, was the striking difference observed between the total number of cases of pneumonia reported and the number of deaths seen in recent years. In his own city of Philadelphia Reimann found a remarkably constant morbidity from pneumonia; that is, the total number of reported cases showed only minor annual fluctuations. The same, however, was not true of the number of deaths from this disease. These showed a sharp drop between 1936 and 1938 and again after 1944.

These general trends, with respect to pneumococcal pneumonia, were also observed on Reimann's own service at the Jefferson Hospital.[3] The number of admissions for pneumonia per thousand patients admitted for all causes was the same in the period January, 1937, to January, 1940, and ten years later during the period October, 1946, to October, 1949. On the other hand, the case-fatality rate in the former period was more than three times that observed in the latter period (21.3 per cent and 6.6 per cent, respectively).

This trend in mortality from pneumococcal pneumonia is just as strikingly illustrated in data recently published by Dowling and Lepper.[4] They surveyed the cases that had received various types of treatment in recent years at the Gallinger Municipal Hospital in Washington, D. C. Those treated with specific antiserum had a case-fatality rate of 16.9 per cent; those treated with sulfonamides had a mortality of 12.3 per cent; and the mortality in patients treated more recently with penicillin, aureomycin or terramycin was only 5.1 per cent. There were about 1000 cases in each group; these figures were compared with a case-fatality rate of 30.5 per cent reported in a similar number of patients from other municipal hospitals among patients who had received no specific treatment.

This general downward trend in mortality from the successive types of new therapeutic agents was noted by Dowling and Lepper to occur in all age groups. However, in the patients who were over sixty years of age, the case-fatality rate was more than 50 per cent among those who received no specific therapy, and there was still a mortality rate of about 15 per cent with the use of the newer antibiotics.

It therefore seems reasonable to conclude that pneumonia is still an important disease and that the total number of cases may not have changed strikingly. However, a larger proportion of cases of milder, atypical pneumonias is now recognized, and the mortality from the classical lobar or pneumococcal pneumonias has dropped strikingly. There is still, nevertheless, a significant mortality from pneumococcal pneumonia among the aged.

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AMENDING BRITAIN'S HEALTH SERVICE

THE Amending Acts Committee of the British Medical Association, after fifteen months' study of the National Health Service Acts of 1948, this fall presented to the Council of the Association its recommendations for changes in the Service. On the whole, despite discontent and grumbling, particularly on the part of the hard-hit general practitioners, the profession has tried to make a go of the situation that it unwillingly accepted three and a half years ago.

For various reasons the Service, as it stands, cannot function in a satisfactory manner, and the Amending Committee, so far as it is within its capacity, has presented recommendations for necessary improvements. The decision to give this group the status of a standing committee of the Association is considered evidence of the general dissatisfaction with conditions of practice under the Acts and of the necessity for continuing reforms.

There is no question of any attempt at engineering the repeal of the Acts; Britain has gone too far down the road to back out, whatever party may be in power. The purpose of any change is to make the Service more effective for the people, more economical for the nation and more tolerable for the doctors who must do their work according to its provisions.

One of the main sources of concern on the Appointed Day in July, 1948, when the Acts went into operation, remains a cause of concern today: namely, the far-reaching and uncontrolled powers of the Minister of Health. Important among these is his authority to regulate the remuneration of those working in hospitals. There is an apparent way of settling disagreements by arbitration, but since those working in hospitals are employees of the Crown while so employed, it makes the Crown, as the *British Medical Journal* points out,* "a judge in its own case, which is something, as learned counsel puts it, 'against natural law'."

The correction of this gross defect would be an amending act providing for a national-health-service court of arbitration to which ministers or hospital management or staff could refer disputes on the various terms of service.

In all, twenty-six recommendations for the immediate modification of the Service have been presented. Of considerable importance, in addition to the curtailment of the powers of the minister, are the proposed election of hospital management committees rather than their appointment by regional hospital boards, as at present, and the delegation to them of greater executive powers as well as financial authority. Another proposed amendment to the Acts would permit patients who receive their medical care privately to obtain drugs and appliances on the same terms as patients registered in the National Health Service. Their present exclusion from this benefit, — for which they are nevertheless heavily taxed, — constitutes a penalty imposed on private practice.

The over-all object of the Amending Acts Committee is to make the service not only more economical but one in which the entire profession can cooperate with some degree of pride and satisfaction. As the *British Medical Journal* states:

> . . .until it has been overhauled we shall not be able to say either to the people in this country or to the rest of the world that the National Health Service is a success. In fact, unless its finances are reorganized it will turn out to be a costly failure, and it is to everyone's interests to see that this is not so.

The western world can today afford no costly failures in the practice of medicine or in any other of its undertakings, on either side of the Atlantic.

*Leading Article. Amending the N. H. S. Acts. *Brit. M. J.*, Oct. 13, 1951.

SYNTHETIC ESTRONE

A SUBSTANCE used in the manufacture of high explosives has now, according to the University of Wisconsin News Service, a new function related to its detonative properties only by inference.

Phenol, known even better to followers of the healing art for its disinfectant and toxic than for its disruptive qualities, can now be used in the production of synthetic estrone. Though far removed from its original relation to sterilization, this novel use for carbolic acid may suggest certain toxic connotations that are, perhaps, something apart from the fury of its blast.

Who knows, when such a new and inexpensive substitute for the female sex hormone is available, how many more and mightier ships can then be launched or towers of Ilium made to blow their tops?

Medical Attendance on Families by the Year. — *. . .You may bargain with your grocer, your butcher, your laundress, and no harm comes of or by it; but for an honorable, an educated physician, to hire himself by the year, like a slave; to pledge his talents and his services, for a stipulated sum, is in direct violation of the ethics of the profession, and indicates at once an unwillingness to enter the field of fair and honorable competition with his brethren.* — New Orleans Med. and Surg. Journal.

Boston M. & S. J., *January 28, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GARRICK — Nathan H. Garrick, M.D., of Boston, died on January 2. He was in his sixty-seventh year.

Dr. Garrick received his degree from Boston University School of Medicine in 1915. He was a fellow of the American Medical Association.

His widow and a son survive.

PHIPPEN — Hardy Phippen, M.D., of Salem, died on January 7. He was in his ninetieth year.

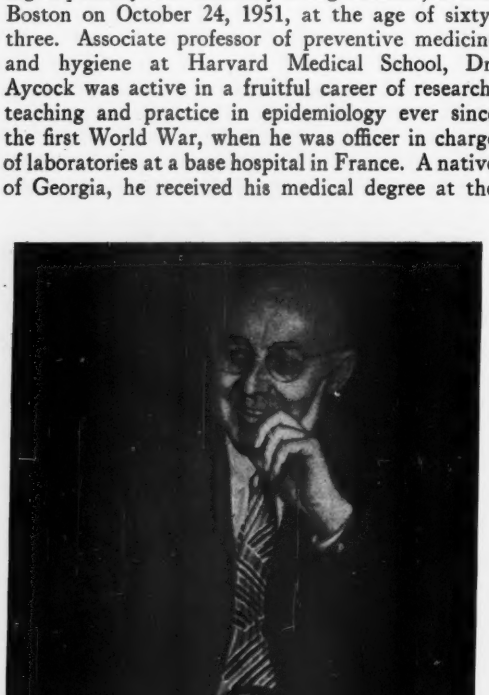
Dr. Phippen received his degree from Harvard Medical School in 1889. He was a member of the American College of Surgeons and the New England Surgical Society and a fellow of the American Medical Association.

A brother survives.

OBITUARY

WILLIAM LLOYD AYCOCK
1889-1951

W. Lloyd Aycock, who in the course of the past thirty-five years contributed more to our understanding of poliomyelitis than any living scientist, died in Boston on October 24, 1951, at the age of sixty-three. Associate professor of preventive medicine and hygiene at Harvard Medical School, Dr. Aycock was active in a fruitful career of research, teaching and practice in epidemiology ever since the first World War, when he was officer in charge of laboratories at a base hospital in France. A native of Georgia, he received his medical degree at the



WILLIAM LLOYD AYCOCK, M.D.

University of Louisville, interned at the New York Postgraduate Hospital and subsequently became instructor in bacteriology at the New York Postgraduate Medical School.

"In my intern days," he once wrote, "the old habit of following my nose instead of orders dogged me. . .I spent too much time working out the Arneth count. . . and Wright's negative phase following typhoid vaccination, and many other things long since gone by the board." However that may be, his intern's experience with clinical disease, coupled with his wartime experience in the field and in the laboratory, led him to break through the tightly compartmented sciences of clinical medicine, bacteriology, immunology, pathology, serology, physiology and genetics into an open sea of research. To embark on his odyssey he needed both a compass to guide him and a ship in which to set sail. His lodestar became poliomyelitis and his vessel was epidemiology. He was a self-trained explorer; when once asked under whom he had studied epidemiology he deliberated a moment and said: "I guess it must have been Hirsch." He lived with Hirsch's *Handbook of Geographical and Historical Pathology* as a self-taught lawyer once lived with Blackstone. He was a prolific reader in general and was particularly delighted whenever he found contemporary medical thought anticipated by a century or two.

Appointed director of the research laboratory (for investigation in poliomyelitis) of the Vermont State Board of Health in 1919, Aycock commenced a series of family studies that led him to anticipate by many years the modern concern with factors other than the virus that determine the outcome of exposure — "why so many get the virus and the virus gets so few," as he put it to students. Solid confirmation of his work emphasizing the importance of autarceologic or host factors, — endocrine, systemic and local, — came in late years. One such study of the relation between tonsillectomy and bulbar poliomyelitis, along lines he drew twenty years ago, was recently published in the *Journal of the American Medical Association.*

Lloyd Aycock was not an epidemiologist exclusively preoccupied with one disease. Quite the reverse; he utilized his extensive knowledge of poliomyelitis as a model for the development of epidemiologic principles underlying both mass disease and specific conditions having as little in common clinically as leprosy and meningitis or congenital deformities and Landry's paralysis.

It is unusual for a pioneering physician to receive full recognition in his lifetime. However, such evaluation did come to Lloyd Aycock when in 1948 an editorial in the *American Journal of Public Health* paid tribute to his achievement as an epidemiologist under the title "What is Epidemiology?" The science was defined as "something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation. To this sort of epidemiological thinking, Aycock and his group at Harvard have made notable contributions during recent years. . . in his emphasis on the importance of climate and seasons (environment) on the prevalence of disease. . .as well as autarceological influences."

Those students who knew Lloyd Aycock in informal seminar teaching or even in everyday conversation about a common interest knew him at his best. They met a keen mind, adept at argument and repartee. He enjoyed an anecdote, especially when it illustrated his point — "— and I'll tell you why," he would add, with a flourish of

his forefinger. One such yarn concerned an old Negro, Uncle Dad Martin, who had no knowledge of ever having had infantile paralysis, to say nothing of poliomyelitis, but did admit to being lame in one leg. Since he was nearly eighty-five at the time he was questioned, his recollections of boyhood days were somewhat hazy — except that he had "jes' had a cold dat settled in de leg; firs' ah got stiff and den it got limbah, an' ah jes' nevah did walk no mo' " — probably as succinct a description of the disease as ever given.

Lloyd Aycock was scientific, objective and as rigorously critical of his own work as of others'. He could shrug off being wrong in an overextended hypothesis as indifferently as a star baseball player reacts to being thrown out at second base, but he was scathingly intolerant of humbug or chicanery in any form. He kept his youth and even precious moments of his childhood to warm his adult years. "I think the event which finally elevated me permanently to the high scientific bracket, and relegated me equally permanently to the low income bracket, was a business transaction with one of my playmates. One day I took my newest possession and obsession — a resplendent red trolley car — over to his house to play. He brought out a little microscope, and how I wanted that microscope! I knew it was poor business to swap such a large trolley car for such a small microscope, but. . .I went with my trolley car, and came back with the microscope. . . With it I put van Leeuwenhoek to shame. I looked at grains of sand (geology). . .fireflies (atomic energy)... sugar and salt (chemistry); and right on the brink of scientific medicine I looked at Epsom salts, trying to see how so little could do so much. . . . Once in a while I still get out that microscope and repolish it and its mahogany case."

Lloyd Aycock was so busy working and writing and talking and reading that he never had much time to dwell on the infirmity of his later years, so nothing need be said of it here. He conquered it with simple homespun courage, a capacity to laugh at himself and a contagious friendliness that will long be remembered.

CIVIL DEFENSE

REPORT OF PROGRESS

By matching federal grants of $720,000, Massachusetts, in the opinion of John F. Stokes, Director of Civil Defense, and Dr. Vlado A. Getting, Commissioner of Public Health, has made a start on a program sufficient for the Commonwealth's needs in the event of atomic attacks and consequent casualties possibly numbering hundreds of thousands.

The $720,000 allotted by the Federal Government, plus an equal amount appropriated by the State, will be used for the purchase of medical supplies to equip first-aid stations. An additional appropriation of $153,000, matched by an equal Federal grant, will be used for the purchase of equipment and supplies to be used in training personnel in all aspects of civil defense.

The State has appropriated an additional $134,000 for adding a second floor to the Hyams Laboratory and $50,000 for a blood-typing program. Thus a total of $1,930,000 has been made available.

The additional space in the Hyams Laboratory will permit the stockpiling of biologic products, blood plasma and fractions of plasma. The blood-grouping and Rh-typing program will provide a list of potential blood donors required to produce the large quantities of blood needed for the proper treatment of casualties.

Director Stokes has advised Budget Commissioner William H. Bixby that additional matching funds may become available, as some states to which funds have been allocated by the Government have not accepted them. Should these grants be offered to Massachusetts, the number of first-aid stations could be increased, if the funds were matched by a General Court appropriation.

The following breakdown shows the sources and contemplated expenditure of the funds:

Description	Federal Funds	State Funds	Total
Antibiotics	$ 54,000	$ 54,000	$ 108,000
Blood donor–recipient sets	326,000	326,000	652,000
Instrument sets	9,000	9,000	18,000
Blood typing	none	50,000	50,000
Hyams Laboratory	none	134,000	134,000
White goods	100,000	100,000	200,000
Paper blankets	31,000	31,000	62,000
First-aid equipment	200,000	200,000	400,000
	$720,000	$ 904,000	$1,624,000
Training equipment for all all divisions of civil defense	153,000	153,000	306,000
	$873,000	$1,057,000	$1,930,000

BOOK REVIEW

Injuries to the Ankle. By J. Grant Bonnin, M.B., B.S. (Melbourne), F.R.C.S. (England). 8°, cloth, 412 pp., with 399 illustrations. New York: Grune and Stratton, 1950. $9.75.

The author has written an exhaustive treatise on injuries about the ankle joint. A historical survey of early writing on the ankle joint and a review of the anatomic relations is followed by a description of the mechanics that produce the various kinds of injuries. The lesions found about the ankle joint are classified as ligamentous injuries without fracture; diastasis of tibia and fibula; fracture by external rotation, abduction, adduction, plantar flexion, dorsiflexion and compression; compound fractures; dislocation; and epiphyseal injuries.

The bimalleolar x-ray film after injuries in this region is considered to be the most important. This is an anteroposterior view of the ankle joint with the foot internally rotated 30 degrees. A hypermobile ankle joint is found in 4 per cent of all uninjured ankles; the sole of the foot can be turned to form a right angle with the ground. Such ankles are prone to various types of ligamentous injury, as their protection is almost entirely muscular. Methods of treatment for injuries about the ankle, — plaster casts and operative procedures, — are described. The author has drawn heavily on his large experience in London hospitals. Pertinent references are given at the end of each chapter. The sketches and photographs are excellent. This book, although written in great detail on so small an anatomic area, does not deal in trivia. It is authoritative. It should be a most valuable book for the orthopedic surgeon.

John G. Kuhns, M.D.

NOTICES

ANNOUNCEMENTS

Dr. George K. Fenn announces the association of Dr. Charles Phillip LeRoyer, Jr., in the practice of internal medicine at 8 Endicott Street, Beverly.

Dr. Charles L. Sullivan announces the removal of his office to 1180 Beacon Street, Brookline.

AMERICAN COLLEGE OF SURGEONS

A two-day Sectional Meeting of the American College of Surgeons will be held at Chalfonte–Haddon Hall in Atlantic City, New Jersey, on February 11 and 12. Papers, panels and symposia on current surgical problems will be presented, and extensive programs for specialists in ophthalmology and otorhinolaryngology have been prepared for February 12. New surgical motion pictures and a stereoscopic colored film on "Radical Resection for Carcinoma of the Stomach" will be shown.

Hotel accommodations may be obtained by writing to Mr. George J. Turcotte, Reservation Manager, Chalfonte–Haddon Hall, Atlantic City, New Jersey.

BETH ISRAEL HOSPITAL MEDICAL SERVICE

A lecture will be given, under the auspices of the Medical Service of the Beth Israel Hospital, on January 30, at 8:30 p.m., in the Sherman Auditorium of Beth Israel Hospital, by Dr. Paul A. Owren, professor of medicine at the University of Oslo and chief of medicine at the Rikshospitalet, Oslo, Norway. The subject will be "The Pathogenesis of Macrocytic Anemias."

Dr. Owren, who occupies the leading chair of medicine in Norway and who has been invited to visit this country by the Josiah Macy Foundation, is distinguished for his work on new clotting factors and for his recent studies of anemia.

THE NEW ENGLAND CARDIOVASCULAR SOCIETY

The next meeting of the New England Cardiovascular Society will be presented by the Beth Israel Hospital and the Massachusetts Memorial Hospitals on Monday, February 4, at 8:00 p.m., in the Dorothy Quincy Suite of John Hancock Hall, 180 Berkeley Street, Boston.

PROGRAM

BETH ISRAEL HOSPITAL (Herrman L. Blumgart, M.D., presiding)

Electrokymography in Myocardial Fibrosis. Dr. Felix Fleischner.

Use of Protoveratrine in Hypertensive Emergencies. Dr. Edward Meilman.

Cardiac Rupture — A Clinical and Pathologic Study. Drs. Stanford Wessler, Paul M. Zoll and Monroe K. Schlesinger.

Indications and Results of I^{131} in Thyrocardiac Patients. Drs. A. Stone Freedberg and George S. Kurland.

MASSACHUSETTS MEMORIAL HOSPITALS (James M. Faulkner, M.D., presiding)

Cardiovascular Adjustments in Anemia. Drs. J. Donald Hatcher, Meyer H. Halperin, Walter E. Judson and Joseph R. Stanton.

The Blood-Pressure Response to the Valsalva Test in Congestive Heart Failure. Drs. Walter E. Judson, Paul Stucki, J. Donald Hatcher, Franklin Epstein and Robert W. Wilkins.

Preliminary Observations on *Rauvolfia Serpentina* in Hypertensive Patients. Drs. Robert W. Wilkins, Walter E. Judson and Joseph R. Stanton.

Interested physicians, medical students, and members of the New England Postgraduate Assembly are cordially invited to attend.

ROBERT ROESLER DE VILLIERS FOUNDATION, INC.

The Robert Roesler De Villiers Foundation, Inc., a membership corporation established exclusively for charitable, scientific, literary and educational purposes in memory of Robert Roesler de Villiers, offers a prize of $1000 for the most important paper that, in the opinion of the jury hereinafter named, is deserving and makes a significant contribution to the knowledge of the nature, causes, origin, treatment or cure of acute leukemia and allied conditions. Should the jury find that the paper to which it awards the prize is of outstanding importance, the jury may suggest that the prize be increased in proportion to the practical value of the paper to a maximum of $1500.

Should the paper describe a cure or effective therapy the jury may suggest that the prize be increased to a maximum of $5000.

The members of the jury will be Dr. Albert Alder, of Switzerland, Dr. William B. Castle, of Boston, Dr. Jan Waldenstroem, of Sweden, and Dr. Maxwell M. Wintrobe, of Salt Lake City.

Further information may be obtained by writing direct to the foundation at 417 Park Avenue, New York 22, N.Y.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Fifth Annual Postgraduate Course in Diseases of the Chest, sponsored by the Council on Postgraduate Medical Education and the Pennsylvania Chapter of the American College of Chest Physicians and the Laennec Society of Philadelphia, will be presented at the Warwick Hotel, Philadelphia, Pennsylvania, March 24–28. A program covering the entire field of heart and lung disease will be presented.

Physicians interested in attending the postgraduate course are invited to communicate with the Executive Offices, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association announces the following programs in its Evening Lecture Series for the month of February.

Tuesday, February 5 — "Surgical Diseases of the Pancreas," by Dr. R. B. Cattell, surgeon, Lahey Clinic. Discussers: Drs. A. J. A. Campbell and W. A. Meissner.

Tuesday, February 12 — "Present Status of Surgical Therapy in Inflammatory Disease of Ileum and Large Bowel," by Dr. J. H. Garlock, senior surgeon, Mt. Sinai Hospital, New York City.

Tuesday, February 19 — "Intracellular Parasitism in Brucellosis," by Dr. Wesley W. Spink, professor of medicine, University of Minnesota Medical School. Discussers: Drs. Louis Weinstein and Maxwell Finland.

Thursday, February 21 — "Medical Genetics," by Dr. Lawrence H. Snyder, professor of medical genetics, University of Oklahoma Medical School. Discussers: Drs. Louis H. Diamond and Donald H. Jolly.

Tuesday, February 26 — "The Heart and the Thyroid Gland, with Particular Reference to Radioactive-Iodine Therapy," by Dr. H. L. Blumgart, professor of medicine, Harvard Medical School. Discussers: Drs. Earle Chapman, E. B. Astwood and Laurence Ellis.

These programs are held at 7:00 p.m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital.

All interested persons are invited to attend.

LAHEY CLINIC FELLOWSHIP TEACHING PROGRAM

The following symposia will be presented as part of the Lahey Clinic fellowship teaching program, at 7:30 p.m. in the clinic auditorium.

January 30. Symposium on Thyroid Diseases. Drs. Elmer C. Bartels, Richard B. Cattell, George O. Bell, William Meissner and Ferdinand A. Salzman.

February 6. Symposium on the Physiology and Diseases of the Adrenal Glands. Drs. A. Seymour Parker, Jr., Lewis M. Hurxthal and Elmer C. Bartels.

February 13. Symposium on Diabetes. Drs. Rosemary A. Murphy and Frank N. Allan.

February 20 and 27. Symposium on Respiratory Diseases. Drs. Carlton R. Souders, Stewart H. Jones, Herbert D. Adams and David P. Boyd.

March 5 and 12. Symposium on Nonoperative Treatment of Orthopedic Conditions. Drs. G. Edmund Haggart, Frank L. Shipp and George Hammond and Miss Ruth Sweet.

March 19. Symposium on Metabolic Bone Diseases. Drs. Rosemary A. Murphy, Lewis M. Hurxthal, G. Edmund Haggart and Magnus I. Smedal.

March 26. Symposium on Convulsive Disorders. Drs. John B. Dynes, Walter I. Tucker and Donald P. Freshwater.

(*Notices concluded on page xiii*)